

ESC Congress Report 2003

Hotline sessions and Clinical Trial Updates



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You will find daily reports from each of the Hotline Sessions and Clinical Trial Updates, presented by the persons who serve as discussants during the sessions. The report will include a summary of the main findings and a commentary with emphasis on implications for clinical practice.



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Editor

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The comments express the personal opinions of the authors, and do not necessarily reflect the official position of the European Society of Cardiology.

OCTOPUS STUDY: Off pump coronary surgery is recognized as a distinct modality of myocardial revascularization, extensively evaluated in the last decade

Professor Ottavio Alfieri

"A randomised comparison of coronary artery bypass grafting on the beating heart (off-pump CABG) to intracoronary stent implantation and conventional CABG (on-pump CABG) in patients referred for elective coronary revascularisation"

The Octopus Study group is providing us with a randomised clinical trial comparing OFF pump coronary surgery not only with conventional CABG, but also with PTCA and stenting. New information is offered because some of the end points of the study have never been taken into consideration in previous trials. Furthermore, the observation period after the procedure is extended to 12 months.

Results with OFF-PUMP and ON-PUMP are similar at 1 year with regard to death, myocardial infarction, stroke (fatal and not fatal), repeated revascularization and recurrent angina. Cognitive outcome is also not significantly different in the two groups at 3 and 12 months.

OFF-PUMP surgery, however, is less expensive and more cost-effective (calculations have been made for direct and indirect costs in the hospital and during the first postoperative year).

When OFF-PUMP surgery is compared with stenting, the outcome at one year is similar for death, myocardial infarction and stroke. As expected, patients submitted to stenting require more often revascularization procedures in the follow-up but, at the end of the first year, stenting results in lower cost and higher cost-effectiveness.

All these findings have to be interpreted with caution, taking into account the features of the Octopus Study.

Due to inclusion and exclusion criteria, the study is focused on a low-risk population of patients, in whom a small number of events is expected regardless the type of procedure. As a consequence, possible differences in outcome could not have been detected due to the relatively limited number of patients included in the study. For sure, the results of the Octopus Study cannot be extrapolated to patients with more advanced coronary disease, more severe ventricular dysfunction or a higher preoperative risk. Furthermore, considering that patients have been recruited according to the feasibility of the procedures with similar degree of revascularization, a strong subjective selection bias is introduced, making the interpretation of the results not easy even for a population of relatively low-risk patients.

Finally, with respect to costs and cost-effectiveness, the data cannot be interpreted without considering the substantial local differences in all costs, which might change not only from country to country but also from institution to institution.

TAXUS II: Commentary on IVUS substudy of TAXUS II

Dr. Peter Kearney

TAXUS II was a randomised triple blind trial comparing clinical, angiographic and IVUS outcomes in 266 patients receiving paclitaxel eluting TAXUS stents (half receiving a slow release (SR) and half a moderate release (MR - relatively more rapid) formulation) with 270 matched controls. The clinical superiority of paclitaxel eluting stents was confirmed.

The IVUS sub-study explored three specific questions – (i) vascular healing within and around TAXUS stents, (ii) incomplete apposition after implantation of TAXUS stents and (iii) edge effects following their implantation. Four hundred and eighty patients representing 89% of the study population had matched IVUS analysis post-procedure and at 6 months. Not all patients were included in each of the analyses

IVUS revealed a dose-independent, evenly distributed inhibition of vascular remodelling within TAXUS stents (% in-stent net volume obstruction 28.9% in the control groups relative to 7.9% in both TAXUS arms). There appeared to be a dose dependent remodelling of the persistent area (or plaque) outside the stent, the vessel area increasing by 0.45 mm² in controls, 0.96 mm² in TAXUS SR stents and 1.41 mm² in TAXUS MR stents. When persistent area at baseline (post-procedure) was compared with neointimal hyperplasia at follow-up, no correlation was found between plaque burden and restenosis.

Quantitative angiographic analysis of this patient population confirmed a beneficial edge effect at 6 months. A complex IVUS analysis of quantitative parameters at proximal and distal edges showed no change in vessel area, an increase in plaque area and a small decrease in lumen area (without producing stenosis) in the proximal edge segment in both TAXUS and control stents. In the distal edge segment there was no change in the vessel area and a slight increase in plaque area in TAXUS and controls. However, lumen area decreased only in the control group. Whereas proximally the beneficial effects of TAXUS stents appear to be confined to the immediately adjacent segment, distally the effects appear to extend beyond the stent.

Following the occurrence of late aneurysmal dilatation in some cases treated with coronary brachytherapy, there have been concerns that drug eluting stents might have a deleterious effect on vessel wall architecture, leading to late aneurysm formation and as a consequence late stent malapposition. Analysis sought to determine whether TAXUS stents increased the rate of malapposition and were such cases associated with clinical sequelae. Cases were classified into (i) resolved (present at baseline but not at follow-up), (ii) persistent (at both baseline and follow-up) and (iii) acquired (present at follow-up but not at baseline). There was no evidence that TAXUS stents induced malapposition relative to controls. It was noted to occur more frequently in longer lesions, cases of unstable angina and diabetes. There was no correlation with adverse events, specifically no occurrence of stent thrombosis either early or late in case of malapposition.

Conclusion: The authors conclude that TAXUS stents produced a dose-independent, evenly distributed inhibition of neointima. The clinical significance of what appeared to be a dose-dependent increase in the positive remodelling that occurred around the stent at follow-up is acknowledged as uncertain, but it was concluded that plaque burden was not a predictor of the degree of neointimal hyperplasia nor did it represent a risk for incomplete apposition. Edge stenosis was absent at the proximal edge of TAXUS stents, and an apparent beneficial effect on lumen dimensions was noted distally. Incomplete apposition of stents is rare, not increased in TAXUS stents and when present is not associated with a demonstrable increase in adverse events.

Commentary: This large study provides a unique insight into the structural mechanisms of the positive clinical effects of TAXUS stents. The data concerning neointima formation is robust, biologically plausible and very convincing. The possibility that there is a dose-dependent increase in plaque burden surrounding TAXUS stents is intriguing, and counters fears that drug elution might lead to harmful thinning of the surrounding structures. I would caution against reading too much into this observation which for technical reasons might be less robust – further studies to confirm are required. Late malapposition represents a fascinating phenomenon which does not occur more frequently with TAXUS stents, and more probably reflects resorption of unrecognised mural thrombus compressed between stent and underlying plaque or within an ulcer cavity than resorption or remodelling of other tissue types.

CHARM programme: Candesartan in heart failure

Professor P.A. Poole-Wilson

The CHARM programme of three trials, evaluating whether candesartan is beneficial in the treatment of patients with heart failure, is decisive, encouraging and yet tantalizing.

This is the third large research programme, and possibly the last, designed to determine the efficiency and safety of a class of drug (angiotensin receptor blocker, ARB) against placebo patients with heart failure. The earlier two were ELITE II and Val-Heft.

The drug used, candesartan, is a powerful ARB and was used in a dose expected to inhibit fully the angiotensin II receptor.

When all patients in all three trials were considered together, there was a strong trend to a reduction in overall mortality. In patients with enlarged hearts, total mortality was significantly reduced. A small increase in fatal cancer was probably a chance event.

The programme was made up of three trials. In the first CHARM ALTERNATIVE the primary endpoint of cardiovascular death and hospitalisation for heart failure was reduced (PC 0.0004). This reduction was largely led by a lower number of hospitalizations. Together with earlier data from other trials, this evidence strongly supports the idea that patients intolerant of an angiotensin converting enzyme inhibitor (ACEi) should be treated with an ARB. Angioedema did not recur in those with this complication when on an ACEi.

CHARM ADDED also reached its primary endpoint (P=0.011) and there was a reduction in cardiovascular death (P=0.029). Thus an ARB can be usefully added to treatment with an ACEi. Importantly there was benefit in patients already on an ACEi and a beta-blocker and in patients on the recommended (top) dose of an ACEi.

A sizeable group of patients are those in whom the symptoms of heart failure are present, but the heart is not enlarged. CHARM PRESERVED did not show benefit, but a trend towards a reduction in hospitalisation. There was a higher rate of drug discontinuation. This type of heart failure is difficult to treat and remains so. CHARM PRESERVED is the first large study to include only this type of patient.

CHARM is a major study, the results of which have been awaited by physicians for some years. The findings extend our knowledge and the clinical indications for the use of ARBs and candesartan in particular.

SPORTIF III: Comments on SPORTIF III

Prof. Werner Klein
Graz, Austria

Session Name: **Stroke prevention using the oral direct thrombin inhibitor ximelagatran, compared with dose-adjusted warfarin in patients with non-valvular atrial fibrillation (SPORTIF III)**

The SPORTIF III final results on stroke prevention using the oral direct thrombin-inhibitor ximelagatran in patients with nonvalvular atrial fibrillation were presented.

The most important findings of the study are that the new oral direct thrombin-inhibitor ximelagatran in a fix dose of 2 x 36 mg/d is a promising alternative to warfarin in patients with nonvalvular atrial fibrillation.

Ximelagatran reduces the risk of stroke in patients with high risk in atrial fibrillation, is much easier to handle, has a lower rate of bleeding complications than warfarin and was generally well-tolerated and safe.

The positive results are driven by are a reduction in ischemic strokes. There is no difference in systemic emboli or transient ischemic attacks and there is no difference between ximelagatran and warfarin regarding secondary events like myocardial infarction or death.

This is in contrast to the findings of the ESTEEM randomized controlled trial which was also presented during the meeting by Lars Wallentin ([Lancet, published online September 1, 2003, PDF](#)). In this higher risk post-myocardial infarction patients, a reduction of the composite endpoint (death, non-fatal myocardial infarction, recurrent ischemia) was found.

The limitations of the study are that it is an open labelled study with blinded assessment and that ximelagatran proved to be not inferior to warfarin, but according to the intention to treatment was not significantly superior. The number needed to treat is 143 patients per year with ximelagatran instead of warfarin in order to prevent one stroke.

There are more liver enzyme elevations with the new drug which were transient and the second confirmatory study is needed and underway (SPORTIF V). The main obstacle against the new drug is probably the cost.

How to implement in clinical practice? The place for the new drug ximelagatran in atrial fibrillation patients is atrial fibrillation patients with high risk for stroke that are not suitable for warfarin, for instance, due to difficulties in monitoring, in noncompliance, especially elderly patients and those with interactions with other drugs or food.

In summary, the new drug ximelagatran could be used instead of warfarin in patients with atrial fibrillation and high risk for stroke (prior stroke or TIA, hypertension on treatment, reduced left ventricular function, age > 75 yrs, coronary artery disease, according to the ACC/AHA/ESC Guidelines for the Management of Patients with Atrial Fibrillation [JACC 2001; 38:1266i-lxx]) especially if there is difficulty in monitoring of warfarin in non-compliant patients or if there are interactions with other drugs or food.

ESTEEM: Efficacy and safety of long-term treatment with the oral direct thrombin inhibitor ximelagatran, in combination with acetylsalicylic acid, in patients after acute myocardial infarction

Freek W.A. Verheugt

The ESTEEM team should be congratulated with the positive results of their large multicenter trial. ESTEEM shows that a novel oral anti-thrombotic therapy is effective in protecting patients following myocardial infarction.

ESTEEM proves the concept of novel oral anticoagulant therapy in the post-infarction patient. Classic oral anticoagulation with vitamin K antagonists has shown to be effective against reinfarction and stroke, even in the aspirin era. In over 21,000 patients in 7 randomized studies the effect of vitamin K antagonists plus aspirin versus aspirin alone was analyzed and found to reduce death and myocardial infarction with 11% ($p < 0.0001$), but at the cost of 60% more major bleeding. In the 5 trials where INR was over 2.0 (5,417 patients) the benefit was much larger (26% risk reduction, $p < 0.0001$), but at a risk of 3 times more major bleeding. These positive results have been obtained with frequent INR monitoring, but oral direct thrombin inhibition does not seem to need therapy monitoring.

In fact, 3 major questions remain:

1. *Why was there in ESTEEM no dose response in efficacy, but there was in bleeding and liver function abnormalities?*

This is not new. In de PENTUA trial evaluating pentasacharide (4 doses) versus enoxaparin it was shown that only the lowest dose was significantly better than enoxaparin and that the higher the dose of the pentasacharide was the least the effect. The same was seen in the CARS trial where fixed dose warfarin was used and 3 mg warfarin daily was not better than 1 mg warfarin daily. Only the INR in the vitamin K antagonist trials has shown to be a predictor of efficacy and safety.

2. *What is the position of ximelagatran in relation to clopidogrel in patients surviving myocardial infarction?*

This is a very difficult question, since there are no comparative data. Therefore, a trial should be initiated where ximelagatran will be directly compared to clopidogrel in patients who have survived a myocardial infarction and are chronically treated with aspirin. Or, ximelagatran should be tested on top of clopidogrel against clopidogrel alone in the same category of patients.

3. *Why does ximelagatran lead to very significantly liver enzyme abnormalities?*

This can be more or less compared to the problems seen with statins. However, of statins we know that liver failure is not existent, for ximelagatran this remains an open question. So far, ximelagatran therapy should be accompanied by frequent liver function testing. Here a major draw back appears, since one of the potential benefits of ximelagatran is the absence of therapy monitoring like INR.

In conclusion

After the positive results of SPORTIF-III in atrial fibrillation, ESTEEM is the second large trial which shows benefit of novel oral anticoagulant therapy. Of course, the results of ESTEEM should be confirmed in further trials. Possible future use of this interesting agent is a. more early administration in acute coronary syndromes with or without reperfusion therapy, b. in the cath lab and c. in patients who carry artificial heart valves.

DECOPI: A randomised trial of occluded artery angioplasty after acute myocardial infarction

Professor E. Braunwald

Since the 1980's, we and others have been interested in the open artery hypothesis, i.e. late opening of an occluded IRA can improve outcome even though there is no or little salvage of ischemic myocardium. There is substantial evidence from animal experiments and observational studies to support this hypothesis.

Slide 1

Prior to DECOPI four small trials tested this hypothesis, by randomizing patients to PTCA or medical therapy. These four trials together randomized a total of only 264 patients. The results were conflicting; two trials showed no significant differences between the treatment arms for both ventricular function and clinical outcome. One trial showed superiority of PTCA, and the fourth showed that late PTCA was inferior to medical management.

Trial	n	Vent. Function	Clinical Outcome
TAMI 16	71	NSD	NSD
TOMIIS	34	NSD	NSD
Horie	83	↑	↑
TOAT	68	↓	↓
	264		

Adapted from Sadrizadeh, S. Am. H. J. 2001;142:411

NSD= no significant difference
↑ improved
↓ worse

DECOPI

- Enrolled < 1/3 of planned number, but still largest single trial to date (212 pts.)
- First "modern" trial with 80% stents
- No effect on 1° end point

Does DECOPI kill Open Artery Hypothesis?

Slide 2

NO!!

- Very low risk population
60% SVD, LAD target vessel in 17% (19 pts)
High use of ASA, β-blockade, ACE-I, statins
Composite end point = 3.1% annualized in medical arm!
- Underpowered
- Only 82% in PCI arm achieved TIMI 3 flow

DECOPI, with 212 patients, even though less than one-third of initially planned, is the largest single randomized trial that has studied the open-artery hypothesis. Also, this excellent study was the first *modern* test of the hypothesis, with 80% of patients receiving stents.

As you have just heard from Dr. Steg, there was no evidence of clinical benefit of PTCA which was performed a median of 8 days after the qualifying MI. The question we must now ask is: "Does this mean that the open-artery hypothesis is dead?" I don't think so, although I cannot deny some bias.

Slide 3

DECOPI enrolled a very low risk population. In the PCI arm, two thirds of the patients had one vessel disease and the LAD was the target vessel in only 17% of patients, i.e. a total of 19 patients in the PTCA arm. A high use of ASA, b-blockade, ACE-I and statins in both groups also contributed to an extremely low event rate, so that the primary end-point, which was a composite of cardiac death, non-fatal MI or ventricular tachyarrhythmia, occurred at an annualized rate of only 3.1% in the medical or control arm.

A trial of many thousands of patients would be required to show benefit in such a low risk group. Therefore, at 212 patients DECOPI was greatly underpowered.

Even so –

- PCI showed significantly higher EF at 6 mo.
- PCI showed strong trends to ↓ dyspnea and cardiac rehospitalization
- IRA patency at 6 mo. is a strong predictor of outcome (mortality and EF)

Slide 4

OPEN ARTERY TRIAL (OAT)

PI: Judith Hochman, M.D.; NIH sponsored
3200 pts. (1400 recruited)
3-28 days post MI; PCI + medical Rx vs Rx
FU=2.5 yrs
EF < 50% and/or proximal occlusion of large coronary artery

STAY TUNED!

Despite this very low rate of primary end point events, in the PTCA arm the ejection fraction at six months was significantly higher and there were strong trends for reduced dyspnea and cardiac hospitalization. Most important, IRA patency at 6 mo. was a strong predictor of outcome – mortality and EF.

Where then do we go from here to study the open-artery hypothesis?

I believe that there are three requirements for an adequate trial:

- 1) A much higher risk population; i.e. with both depression of LV function and a high incidence of predominant LAD disease;
- 2) A much larger sample size than DECOPI;
- 3) Use of even more modern PCI techniques and stents that will increase the TIMI 3 flow rate above the 82% achieved in DECOPI, and that reduce reocclusion/restenosis below the observed 59%.

Slide 5

Fortunately, the Open Artery Trial (OAT), which is now ongoing, meets some of these requirements. This trial is led by Dr. Judith Hochman of NY and has now enrolled more than 1400 of a planned 3200 patients 3-28 days post AMI. These patients are regarded to be at high risk because of an impaired EF or proximal occlusion of a large coronary artery.

I congratulate Dr. Steg and his colleagues on their conduct of a very fine trial and contributing useful information to this important hypothesis. I would be interested in learning, whether, despite the small size of the overall trial, the outcome differed in the higher and lower risk subgroups. Also, I wonder what the Holter and signal-average ECG showed? The results of OAT are still at least four to five years away. In the meantime what should we do with the many AMI patients worldwide who do not receive early reperfusion? Given the totality of information, including experimental and observational studies, I recommend assessment of LV function in all patients who have not received reperfusion therapy but who are potential candidates for revascularization, followed by coronary arteriography in those with depressed LV function. In such patients, it is quite reasonable to open totally occluded arteries if they are large, proximal and their territories include large portions of the left ventricle.

GRACIA-2: Primary optimal percutaneous coronary intervention versus facilitated intervention (tenecteplase plus stenting) in patients with ST-elevated acute myocardial infarction

Prof. F. Van der Werf

GRACIA-2 results favour a strategy of a combined pharmacological-mechanical approach to patients with an acute myocardial infarction

In the GRACIA-2 trial a relatively small population of 212 patients with STEMI (≤ 12 hours of symptom onset) was randomised between immediate (within 3 hours) primary PCI of the infarct-related coronary artery (N = 108) or a strategy of facilitated revascularization, that is, immediate thrombolysis followed by early (between 3 and 12 hours) angiography and, if indicated, by optimal revascularization (PCI or CABG). In the thrombolysis arm patients were given TNK-tPA and enoxaparin, in the primary PCI arm stenting was performed under protection of abciximab.

The primary end points were infarct size (measured as the area under the CK-MB and TnT curves), proportion of patients with complete ST-segment resolution and LV function measured angiographically at 6 weeks.

No significant differences were observed in infarct size or LV function. Significantly more patients in the facilitated revascularization arm had complete ST-segment resolution at 6 hrs (61% vs. 43.2%, $p = 0.03$).

Important clinical outcomes were in favour of facilitated revascularization: death at 6 weeks: 3% vs. 6% and major bleeding (including ICH): 2% vs. 3%. However, there was a slight excess in reinfarction and readmissions (2% vs. 1% and 11% vs. 9%, respectively) with this approach.

The results of this study are in support of the concept of a combined pharmacological-mechanical approach to patients with a STEMI and are in agreement with the observations made in CAPTIM. Whether this approach should be generalized and which pharmacological therapy should be preferred are the topics of ongoing large trials such as FINESSE, CARESSSE, ADVANCE-MI and ASSENT-4.

COMPANION: a cornerstone study in the validation process of cardiac resynchronisation therapy?

Prof. J-C. Daubert

Session name: Cardiac resynchronization therapy reduces hospitalizations and cardiac resynchronization therapy with an implantable defibrillator reduces mortality in chronic heart failure (COMPANION)

Previous randomized controlled studies (MUSTIC and MIRACLE) have shown that cardiac resynchronization therapy (CRT) significantly improves symptoms and exercise tolerance in advanced heart failure (HF) patients with intraventricular conduction delay, under optimized drug treatment (ODT). The major limitation of these trials was that primary endpoint was only functional. To be definitively validated and thus accepted by the medical community, CRT has to demonstrate additional benefit on morbidity and if possible on mortality in specifically designed large-scale trials. To address this key question, two trials have recently been designed. The CARE-HF study is still ongoing in Europe. The US COMPANION study was recently completed and the preliminary results are presented here. In this trial, CRT ie atrio-biventricular pacing, wether alone or in combination with automatic defibrillation (CRT-ICD) were compared to ODT in a 2:2:1 randomisation plan, the primary endpoint being a time-to-first-event analysis of all-cause mortality or hospitalisation. CRT alone and CRT-ICD significantly reduced the 1-year event rate of the primary endpoint by 19% but only CRT-ICD significantly decreased the 1-year mortality rate by 43% whereas the 23% reduction with CRT alone was not significant.

Several comments can be addressed regarding methodology and results: - the significant difference in the combined primary endpoint between control and CRT groups was principally driven by all-cause hospitalization (>80%) which is a "soft" endpoint in unblinded trials, and a large proportion of admissions were not HF related -13% patients in the ODT group withdrew consent and exited the study and there is no information on their outcome - the results presentation is based on CRF data and not on events adjudicated by the endpoint committee - the lack of pre-planned comparison between CRT-ICD and CRT alone is embarrassing - information on the long term effect of CRT is totally lacking due to the early termination of enrollment and follow-up (mean f/u time:16 months).

In conclusion, the COMPANION trial was the first large-scale study to be designed for assessing the effects of CRT and CRT-ICD on morbidity and mortality in dyssynchronised HF patients. The very encouraging preliminary result has still to be validated by the final data analysis. As COMPANION does not provide any clear information on the global clinical impact of CRT per se, further studies are needed to definitively conclude.

ARTS, SoS, ERACI-2 and MASS-2: Coronary artery bypass surgery versus stenting for the treatment of multivessel disease: a meta-analysis with individual patient data

Dr. Rob Henderson

The optimal myocardial revascularisation strategy for patients with multi-vessel coronary artery disease remains controversial. Marcus Flather and colleagues should therefore be congratulated on their timely individual patient data meta-analysis of recent randomised controlled trials of coronary artery bypass surgery versus multi-vessel coronary stenting. They identified five relevant trials, but excluded one trial (AWESOME) from their analysis because it enrolled only high-risk patients with medically refractory myocardial ischaemia. An additional published trial of coronary bypass grafting versus coronary stenting (SIMA) recruited patients with single vessel disease and was not considered relevant. The meta-analysis therefore includes individual patient data from four trials (SOS, ARTS, ERACI-2, MASS-2), that randomised a total of 3051 patients.

All of the patients in these trials were considered angiographically suitable for percutaneous coronary intervention, over 50% had two-vessel disease, and the majority had preserved left ventricular function. Most of the patients included in the analysis are therefore at moderate cardiovascular risk, and would not be expected to gain major prognostic advantage from coronary bypass surgery.

At one year the combined rate of death, myocardial infarction and stroke (the primary end-point) was similar in the two treatment groups (9.1% versus 8.7%), but the confidence interval for this comparison is quite wide and does not exclude an absolute difference in this event rate of 2%. Interpretation of the analysis is further complicated by significant heterogeneity between the trials. The cause of this heterogeneity is uncertain but might be partly due to differences in end-point definitions, surgical mortality, and baseline unstable angina rates between the trials.

The mortality rates in the bypass surgery and stent groups were also comparable (2.8% versus 3.0%), but with only 3051 patients and one year follow-up this analysis lacks statistical power. In this context the decision to exclude the AWESOME and SIMA trials from the analysis is surprising. For comparison, a randomised clinical trial in which the mortality rate in one treatment group is 3% would require nearly 8000 patients to detect a 33% relative reduction in mortality in the other group (assuming 5% significance and 80% power). Moreover, in a recent meta-analysis of published summary data, which included trials from the pre-stent era, a difference in mortality between patients treated by coronary bypass grafting and percutaneous coronary intervention only became apparent after five years follow-up (see Hoffman et al, JACC 2003;41:1293).

The trials in the meta-analysis, recruited patients from 1995 to 2000 and since then there have been significant advances in cardiological practice. It is now recognised that patients with coronary artery disease may benefit from treatment with medications that include statins and ACE inhibitors. Patients undergoing percutaneous coronary interventions may also benefit from glycoprotein IIb/IIIa inhibitors, but in the meta-analysis only 7% of patients received these agents, even though 28% initially presented with unstable angina. All of the trials in the meta-analysis used early generation bare metal stents, which have now been replaced by improved stent designs and drug coated stents. There has also been progress in the surgical arena, with increasing use of arterial revascularisation and off-pump surgical techniques. All of these advances limit the relevance of the meta-analysis to current clinical practice.

The meta-analysis therefore requires cautious interpretation. In the short term multi-vessel stenting in selected patients appears safe, but a reliable estimate of the effects on mortality, and other major cardiac or cerebrovascular events, requires longer-term follow-up. It is clear that multi-vessel stenting is associated with a slightly higher risk of angina and a four-fold increase in risk of repeat revascularisation within the first year of intervention, and clinicians should consider these observations when discussing the choice of revascularisation procedure with their patients. Further appropriately sized (large) randomised trials are required to fully elucidate the relative effects of contemporary surgical and percutaneous coronary interventions on mortality and morbidity.

EUROPA: Effects of an angiotensin-converting enzyme inhibitor, perindopril, on cardiovascular events in stable coronary artery disease patients

Sidney C. Smith, Jr. MD
North Carolina, United States of America

Professor Kim Fox and his co investigators are to be congratulated on an excellent study in EUROPA. The results of EUROPA should have a major impact on therapeutic preventive strategies in patients with known coronary heart disease.

Little more than a decade ago, the landmark findings of the SAVE trial were published documenting the benefit of ACE inhibitor therapy for patients with reduced ejection fraction after a recent myocardial infarction. Subsequent studies in animals and retrospective analyses of clinical trials involving patients with congestive heart failure have suggested that ACE inhibitors are effective in decreasing ischemic events and lowering the incidence of myocardial infarction. The HOPE trial, which involved high-risk patients with vascular disease, demonstrated significant benefits as a randomized prospective clinical trial among patients receiving the ACE inhibitor ramipril. However, as impressive as the results of the HOPE are in documenting the benefits of ACE inhibitor therapy to reduce cardiovascular events among patients with high risk vascular disease, several important questions remain. These questions include: 1) Are the findings for the ACE inhibitor ramipril used in the HOPE trial transferable to other ACE inhibitors?; 2) Would a trial directed exclusively toward patients with known coronary heart disease but at a lower risk demonstrate benefits similar to those observed for the higher risk population in the HOPE trial?; 3) Are the effects of ACE inhibition somewhat independent of a major reduction in blood pressure?; and 4) Will the effects of ACE inhibition in reducing cardiovascular events occur in a population younger than age 55, the lower limit of inclusion for the HOPE trial.

The results of the EUROPA trial presented at the 2003 ESC Scientific Congress in Vienna establish conclusive evidence for the benefits of the ACE inhibitor perindopril when given to lower risk patients with known coronary heart disease. EUROPA involved 12, 218 patients with documented coronary heart disease, male or female, aged 18 years or older, randomized to perindopril, 8 mg daily versus control and demonstrate a highly significant 20 % reduction in the combined endpoint of cardiovascular death, myocardial infarction and resuscitated cardiac arrest. The benefits are seen across all age groups and among those with and without hypertension, with and without diabetes and among men and women—although the study included less than 15% women. As in the HOPE trial, reduction in vascular events was associated with rather small changes in systolic (5 mm/Hg) and diastolic (2 mm/Hg) blood pressure. Taken together these observations suggest that the benefits of ACE inhibition related to vascular effects occur in addition to those associated with reduction of blood pressure. Importantly, the benefits were seen in addition to other standard therapies which included platelet inhibition (92%), lipid lowering drugs (58%) and beta blockers (62%). Since patients with clinical heart failure were excluded from the trial an unexpected finding in this population was the early and sustained reduction of heart failure, with a relative risk reduction of 39% occurring over the four year period of the trial. However, this was an uncommon finding, occurring in only 1 - 2% of patients.

I believe that the results of EUROPA will be especially valuable in developing therapeutic strategies and guidelines for patients with coronary heart disease. They confirm the benefit of an ACE inhibitor, Perindopril, when given broadly to patients with coronary heart disease as chronic therapy. We are now left with only a few remaining questions which hopefully will be answered by the PEACE trial. These include whether the benefits of ACE inhibition therapy can be extended to patients at lower risk for cardiovascular events and whether they will be seen in a patient group with higher adherence to the preventive therapies of beta blocker and lipid lowering therapy beyond that observed in EUROPA.

Overall the EUROPA trial joins the SAVE and HOPE trials as an elegant demonstration of the value of well designed clinical research in contributing to our knowledge of the benefits of medical therapies, in the case of EUROPA specifically for the ACE inhibitor perindopril as chronic therapy for patients with established coronary heart disease.

***BASEL: Brain natriuretic peptide for Acute Shortness of breath
EvaLuation: a randomized comparison***

Professor Adam Torbicki

Brain natriuretic peptide (BNP) received recently lot of attention as a possible diagnostic and prognostic marker in congestive heart failure. BASEL is a randomized multicentre trial attempting for the first time to assess what is the impact of including BNP in the triage of emergency department patients presenting with acute dyspnea. Treatment time, costs (primary endpoints) and need for hospitalisation as well as re-admission rates and 30 days mortality (secondary endpoints) were compared between, otherwise similar, 227 patients with acute dyspnea managed according to standard clinical practice and 225 patients in whom results of rapid quantitative BNP test was also available. The BASEL trialists found, that implementation of rapid BNP test reduced treatment time (from 13.7 to 10.5 days, $p=0.009$) and costs (7,264 to 5.410\$, $p=0.006$) without adverse impact on mortality or need for readmission.

Several issues in this trial deserve attention. While no specific recommendations were made regarding management of patients according to BNP levels three groups were pre-specified: those with BNP <100, 100-500 and above 500 pg/mL. In this way the authors anticipated and respected the "gray zone" characterised by mildly elevated BNP, which may have a variety of causes and probably requires similar diagnostic workup regardless whether BNP test has been used or not. Such approach should be supported as clearly it increases safety, though probably reduce the overall impact of BNP testing in emergency triage. Unfortunately the current BASEL report does not provide data on the distribution of patients to the three predefined classes, including the "grey zone" category. It also not clear how the money was actually saved in BNP group – was this mostly due to shorter total hospitalisation time or to reduced need for further diagnostic tests, such as echocardiography. This data would be useful also because the trial being - by definition - not blinded theoretically left a possibility of a somewhat faster diagnostic track for BNP subgroup. This could potentially affect hospitalisation time but not the need for further laboratory testing.

The main idea behind pre-specifying three levels of BNP was clearly to exclude heart failure in patients with very low BNP and immediately proceed to intensive treatment of heart failure in those with very high BNP levels. While this approach was save in the hands of BASEL trialist it should be remembered that low BNP levels were reported in dyspnea of very recent (<4h) onset (Logeart *et al. JACC 2002*) and very high BNP (up to 1500 pg/mL) can be found in acute pulmonary embolism (Kucher *et al. Circulation 2003*). Nothing is perfect.

In summary: BASEL trial offers another piece of convincing evidence in favor of implementing a rapid BNP test into our clinical practice. If used with caution it should help us to be more effective and less expensive in managing patients with acute dyspnea.

Syst-Eur: Long-term outcome results of the Systolic Hypertension in Europe trial

Dr. Frank Ruschitzka, F.E.S.C.

Background:

The Systolic Hypertension in Europe (Syst-Eur) Trial recently reported that antihypertensive therapy initiated with the dihydropyridine nitrendipine reduced the risk of fatal and nonfatal stroke as well as cardiovascular endpoints in older patients with isolated systolic hypertension. The present study is an extended follow-up to evaluate the long-term outcome of the Syst-Eur patients and assess safety of chronic treatment with a dihydropyridine in older patients with isolated systolic hypertension.

Strength of the study

This study is important for several reasons. First, it is unique among large randomized studies in showing the organisation of an extended follow-up. Secondly, it is interesting to see how switching the placebo group to active treatment brings the blood pressure in this group to the level of the blood pressure in the original active treatment group, and reduces the event rate to the same level. Antihypertensive treatment decreased the risk of stroke by 39% after 2 years and 28% after 6 years and of cardiovascular events by 28 and 15%, respectively. Hence, the early benefit observed in the placebo-controlled trial was maintained throughout extended follow-up.

Potential Limitations

Because of switching the placebo group to active treatment, there is obviously no control group. Moreover, the groups can not be identical at the start of the extended follow-up phase because of differences in event rate during the double-blind period. Unfortunately, not all potential candidates participated in supervised extended follow-up. As in all randomized clinical trials of patients older than age 60 with systolic hypertension, total mortality was reduced much less, if at all, than was morbidity. In older people. However, the reduction of morbidity that makes life so difficult for the elderly provides a strong rationale for antihypertensive therapy.

How may the trial results be implemented in clinical practice?

Hypertension contributes to as much as 50% of cardiovascular disease in Europe and the United States. Notwithstanding previous randomized clinical trials, particularly with thiazide diuretics, demonstrated that lowering blood pressure reduces cardio- and cerebrovascular as well as renal complications, these findings have not been translated effectively into clinical practice, yet. Indeed, one fourth of the patients with hypertension still remain unaware that they have the disorder, and approximately three fourths of those with known hypertension have blood pressure that exceeds recommended levels. Most cases of uncontrolled hypertension in Europe and the US consist of isolated systolic hypertension in older adults with an age of at least 60 years. Because of the aging population and the greater number of cardiovascular events in the elderly, the total number of deaths from cardiovascular disease will increase substantially unless these elderly patients with mostly isolated systolic hypertension are adequately treated. This underscores the clinical relevance of the present study, as these elderly patients were included in Syst-Eur and its long-term follow-up. Interestingly, the early benefit observed in the placebo-controlled trial was maintained throughout long-term follow-up thus providing further evidence that treatment of isolated systolic hypertension is safe and provides long-term benefit in the elderly.

The new ESC/ESH guidelines favor a low-dose diuretic or a DHP-CCB in isolated systolic hypertension. A recent meta-analysis of all eight published outcome trials in the elderly with ISH, involving 15,693 patients who were followed up for an average of 3.8 years, active treatment reduced total mortality by 13%, all cardiovascular events by 26% and stroke by 30% (calculated number of elderly ISH patients who would need to be treated for five years to prevent a fatal or nonfatal event: 26 for any cardiovascular event and 48 for a stroke).

Some physicians become concerned when a reduction in systolic blood pressure is associated with very low levels of diastolic blood pressure. Although excessive lowering of blood pressure can be a problem, particularly in frail elderly patients, the majority of elderly persons with systolic hypertension tolerate such reductions well. Indeed, the validity of the proposed J-curve phenomenon, in which the risk of vascular complications is increased by low systolic or diastolic blood-pressure levels, is not supported by recent clinical data. In the contrary, cognitive function in the elderly is not impaired and may even be improved by antihypertensive therapy. In Syst-Eur, the incidence of dementia was approximately 50 percent lower in the active-treatment group than in the control group. Unfortunately, the achievement of targeted levels of systolic blood pressure in the elderly often requires the use of more than one antihypertensive drug. Finally, in the enthusiasm to apply these major benefits of therapy to the large population of frail elderly hypertensives, sight should not be lost of the well-documented antihypertensive efficacy of multiple lifestyle modifications.

EPHESUS: Angiotensin-converting enzyme inhibitor and beta-blocker effects on the efficacy of eplerenone

Professor D.V. Cokkinos, M.D

The good results of EPHESUS¹ agree with the previous ones from RALES². Both studies, RALES in 1663 pts and EPHESUS in 6632 pts, all post myocardial infarction showed a significant reduction in mortality when eplerenone in EPHESUS and spironolactone in RALES were added to standard treatment. They can be explained by basic knowledge.

Elevated aldosterone (ALD) produces endothelial dysfunction, LVH, myocardial injury and necrosis, cytokine release, ROS production, increases central sympathetic drive, NE spillover,³ and facilitates ventricular arrhythmias.^{4,5} It also chronically increases LV and aortic fibrosis and adversely affects post MI LV remodeling.⁶ There is evidence that it may be produced locally in vascular tissue. Aldosterone blockade may reverse all these untoward results.⁷ This has been shown definitively in post-MI patients in whom mineral-corticoid receptor antagonism (MRA) inhibited ALD extraction into the heart by 70%. It also suppressed the increase of PIIINP, a biological marker of cardiac fibrosis.⁶

In pts with heart failure, Despite ACE inhibition, both angiotensin II and ALD levels "escape" with the latter showing a more pronounced rebound.^{5,7}

It should be stressed that in EPHESUS¹ 87% of patients were receiving ACE inhibitors or angiotensin – receptor blockers and 75% beta blockers. In this study eplerenone was administered, 7.3±3.0 days after an acute myocardial infarction, while in the study by Hayashi et al,⁶ MRA was effected immediately after the acute infarction.

In RALES², only 11% of patients were receiving beta blockers, although the vast majority (94%) were receiving ACE inhibitors. In Hayashi's⁶ study, all patients were receiving enalapril, but only about 10% were receiving beta-blockers. In EPHESUS¹ eplerenone was found to exert its best action when patients were receiving both families of drugs.

How should these results of EPHESUS¹ be interpreted? Any explanation could be a fruitless pastime since the numbers not receiving any of the two drugs was obviously small. It should be stressed that these were post-infarction patients. Post-infarction both ACE-inhibition and angiotensin receptor blockade are essential. One could argue that MRA and ACE inhibition angiotensin – receptor blockade combined are especially beneficial against unfavorable LV remodeling. Alternatively, one might argue that when both families of protective medications are given, further ALD blockade, eliminating the noxious effects of this substance's rebound, may provide the greatest benefit.

The two mechanisms are additive in other settings.

Aldosterone decreases Na+ K+ pump current (I_p) function; this can be prevented by losartan, a finding consistent with the protective interaction of these drugs.¹⁰

Krum et al.¹¹ showed that in hypertensive patients on ACE inhibition or angiotensin II receptor blockade the addition of eplerenone afforded a more satisfactory antihypertensive effect. The same was actually seen in EPHESUS.¹

Finally, one more interaction which could be operational in EPHESUS¹ should be mentioned: In dogs with severe mitral regurgitation, angiotensin II infusion evoked releases of norepinephrine and epinephrine into the cardiac interstitial fluid space which were attenuated by metoprolol.¹²

Conversely, Canrenone, the active metabolite of spironolactone apart from improving left ventricular remodeling, increased the ventricular fibrillation threshold and decreased myocardial norepinephrine content.¹³

One less known aspect is that spironolactone increases contractility of the isolated rat heart; paradoxically aldosterone does the same, while both agents together further increase contractility.¹⁴

All these data suggest that aldosterone blockade, together with beta-blockade, angiotensin converting enzyme inhibition and /or angiotensin receptor blockade may act synergistically in heart failure, post myocardial infarction, hypertension and left ventricular hypertrophy.

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ON-TIME: Does pre-transportation treatment with tirofiban improve patency in acute myocardial infarction patients who are referred for percutaneous coronary intervention ?

Flavio Ribichini, MD

ON-TIME is a randomized multicenter trial of myocardial revascularization with percutaneous coronary intervention (PCI) in patients with acute myocardial infarction (AMI) treated with tirofiban before PCI.

One group of patients was randomized to the early administration of tirofiban, started during transportation to the catheterization laboratory, and one group received placebo during transportation to the cathlab and started tirofiban late, after the first angiogram.

The primary endpoint of the study was the angiographic TIMI 3 coronary flow at the initial angiogram. Secondary endpoints were the effect of tirofiban pre-treatment on the 4 subcategories of TIMI flow, the effect on the presence of thrombosis and the effect on the final success of the PCI procedure. All angiograms were analyzed by an independent core laboratory. A total of 500 patients were enrolled in the study with the aim of assessing a possible increment of the TIMI 3 flow at the first angiogram from 10 to 20% with early tirofiban administration.

All patients received UFH (5000 IU iv bolus) and aspirin (500mg iv bolus) before transportation. After PCI all were treated with weight adjusted LMWH for 48 hours, clopidogrel 300mg loading and 75mg for 30 days, and aspirin, beta blocker, ACE inhibitors and statins. Tirofiban was given as a first bolus of 0.15 µg/kg/min infusion lasting 24 hours. Females younger than 50, and all patients older than 80, or in Killip class III or IV, or on treatment with oral anticoagulation, or treated with fibrinolysis <24 hours, in hemodialysis, or with contraindications to the use of IIb/IIIa inhibitors were not included. After randomization (41% in the ambulance) patients were immediately taken to a PCI center rather than to the nearest hospital. Mean age was 62 years, 10% of patients were diabetics, 46% had anterior AMI and 16% were in Killip class 2.

Patients-related delay was very short (94'), time from diagnosis to randomization was 25', inter-hospital transportation needed 33', door-to-angiography time was 25' and time from angiography to balloon was 15'. The early group received tirofiban a median of 59' earlier (range 11-178') than the late group, who received the study drug a median of 15' before PCI.

The primary endpoint of the study (TIMI 3 flow at basal angiogram) was not different between the 2 groups (19% in the early group versus 15% in the late group, $p=0.22$). However, patients treated early had significantly less totally occluded vessels (TIMI 0: 44% versus 59%, $p=0.0013$) and less thrombus and fresh occlusions (60% versus 73%, $p=0.002$). These differences were consistent in all patients subgroups. There was no difference as to the final PCI result: TIMI 3 89% in the early group versus 91% in the late group, $p=0.56$, myocardial blush 17 versus grade 3: 51% versus 53%, $p=0.87$, and corrected TIMI frame count: 27.15 versus 15, $p=0.56$ respectively. At 30 days, 11 patients died (2.2%) and only 5 had reinfarction (1%); 1 patient had fibrinolysis-related stroke and 19 had major bleeding (3.7%).

ON-TIME shows that the optimal medical treatment to facilitate PCI in AMI is still not defined. The TIMI 3 flow reported by the investigators is similar to that obtained with the pre-PCI administration of abciximab in the ADMIRAL trial (17%), and lower than the TIMI 3 rate obtained with 1/2 dose of tPA in the PACT trial (33%).

The extraordinary finding of ON-TIME is not associated to the study drug, but to the very short time of patients delay and health-care system reaction. Indeed, patients-related delay is almost half of that of GUSTO V, and door-to-balloon time is less than 50 minutes. This indicates that pre-treatment times can be largely reduced, and this is expected to translate into clinical benefit. Enhancing the awareness of people about the importance of symptoms and about a healthy lifestyle and shortening intervention times will likely save more lives than any other intervention.

ESC Congress Report 2003

Hotline sessions and Clinical Trial Updates



Hotline I

Hot Line 1

- [Effects of an angiotensin-converting enzyme inhibitor, perindopril, on cardiovascular events in stable coronary artery disease patients \(EUROPA\) \(PDF 58Kb\)](#)
- Candesartan in heart failure (CHARM programme)
- Brain natriuretic peptide for Acute Shortness of breath Evaluation: a randomized comparison (BASEL)

Hotline II

Hot Line II

- [Does pre-transportation treatment with tirofiban improve patency in acute myocardial infarction patients who are referred for percutaneous coronary intervention \(ON-TIME\)? \(PDF 18.5Kb\)](#)
- [Primary optimal percutaneous coronary intervention versus facilitated intervention \(tenecteplase plus stenting\) in patients with ST-elevated acute myocardial infarction \(GRACIA-2\) \(PDF 77.5Kb\)](#)
- [A randomised trial of occluded artery angioplasty after acute myocardial infarction \(DECOPI\) \(PDF 19Kb\)](#)
- [Sirolimus-eluting stent in long lesions: direct stenting versus predilatation \(E-SIRIUS\)](#)
- [Outcome of the non-polymeric paclitaxel eluting stent \(DELIVER II\)](#)

Efficacy and safety of long-term treatment with the oral direct thrombin inhibitor ximelagatran, in combination. with acetylsalicylic acid, in patients after acute myocardial infarction (ESTEEM)

Clinical Trial Update I

Clinical Trial Update I

- Year follow-up of the German Angioplasty versus Bypass Investigation (GABI)
- A randomised comparison of coronary artery bypass grafting on the beating heart (off-pump CABG) to intracoronary stent implantation and conventional CABG (on-pump CABG) in patients referred for elective coronary revascularisation
- [Coronary artery bypass surgery versus stenting for the treatment of multivessel disease: a meta-analysis with individual patient data \(ARTS, SoS, ERACI-2 and MASS-2\) \(PDF 171Kb\)](#)
- Vascular responses within and adjacent to polymeric paclitaxel-eluting stent. Novel intravascular ultrasound analyses (TAXUS II)

Sirolimus-eluting stent implantation reduces the incidence of adverse events compared to conventional percutaneous techniques in the "real world": a study of 1600 patients (RESEARCH)

Clinical Trial Update II

Clinical Trial Update II

- Valsartan Heart Failure Trial (VAL-HEFT)
- [Angiotensin-converting enzyme inhibitor and beta-blocker effects on the efficacy of eplerenone \(EPHESUS\) \(PDF 32Kb\)](#)
- The Carvedilol Or Metoprolol European Trial (COMET)
- Cardiac resynchronization therapy reduces hospitalizations and cardiac resynchronization therapy with an implantable defibrillator reduces mortality in chronic heart failure (COMPANION)

Stroke prevention using the oral direct thrombin inhibitor ximelagatran, compared with dose adjusted Warfarin in patients with non-valvular atrial fibrillation (SPORTIF III)

Clinical Trial Update III

Clinical Trial Update III

- Long-term outcome results of the Systolic Hypertension in Europe trial (Syst-Eur)
- The losartan intervention for endpoint reduction in hypertension study (LIFE)
- [The INternational VErapamil/Trandolapril Study \(INVEST\) \(PDF 137Kb\)](#)
- The Anglo-Sandinavian Cardiac Outcomes Trial: Lipid Lowering Arm (ASCOT: LLA)
- Study TO Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM)
- Extended follow-ups of the Heart Outcomes Prevention Evaluation (HOPE-TOO)

EUROPA



EUROPEAN TRIAL ON REDUCTION OF CARDIAC EVENTS WITH PERINDOPRIL IN STABLE CORONARY ARTERY DISEASE

Perindopril 8 mg once daily

Perindopril

4 mg 8 mg

Placebo

-1 -1/2 0

12

24

36

48

60

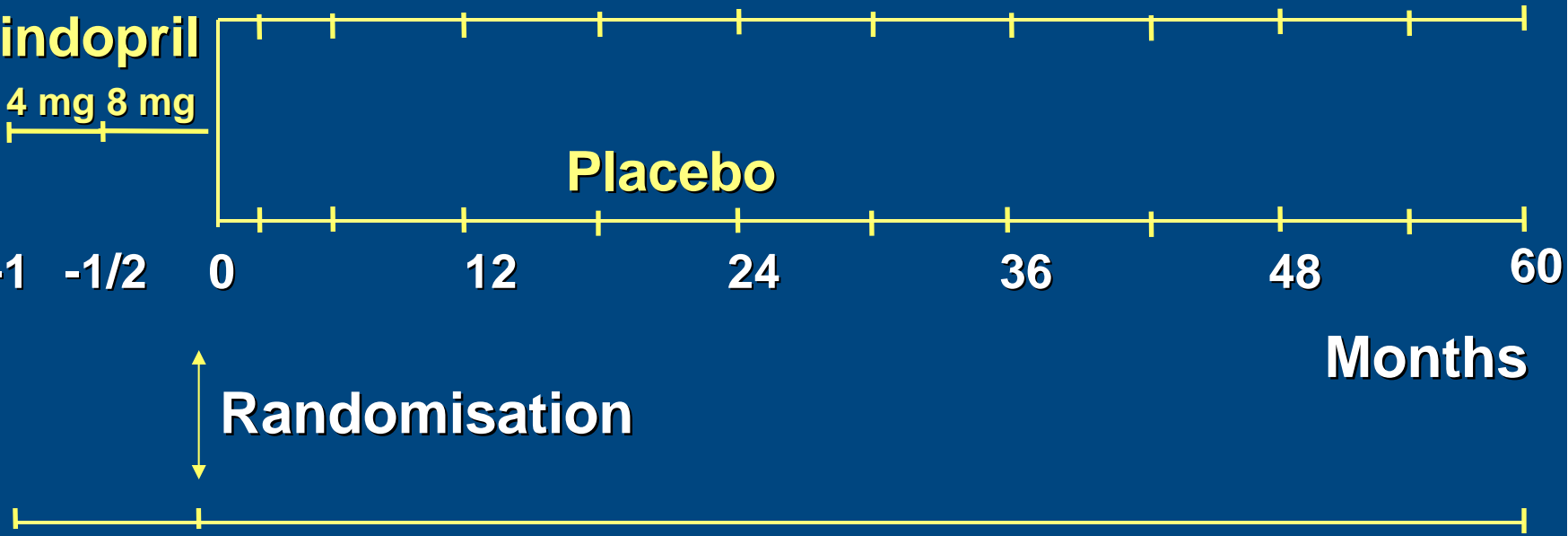
Months

Randomisation

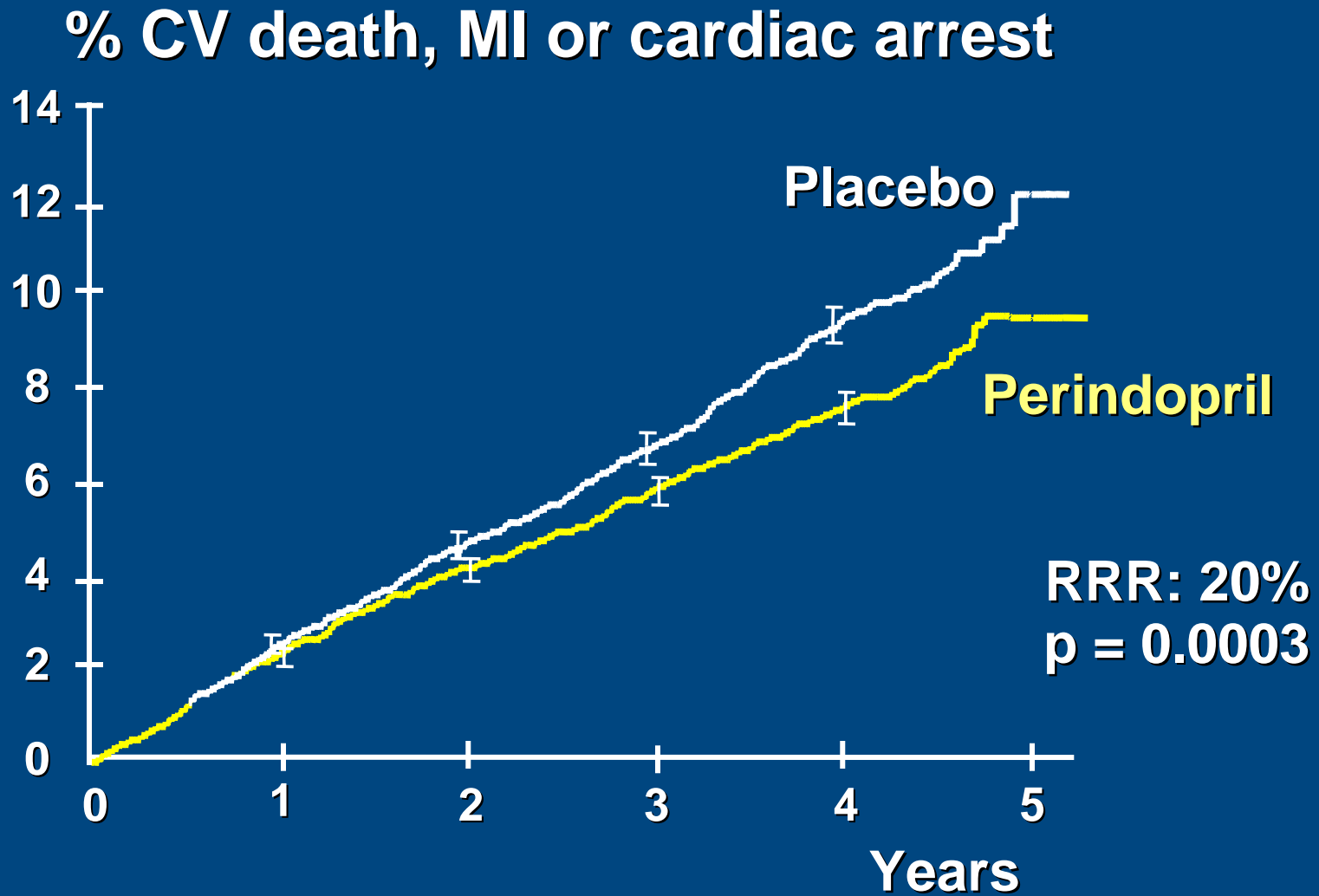
Run-in period

Follow-up

n = 12 218



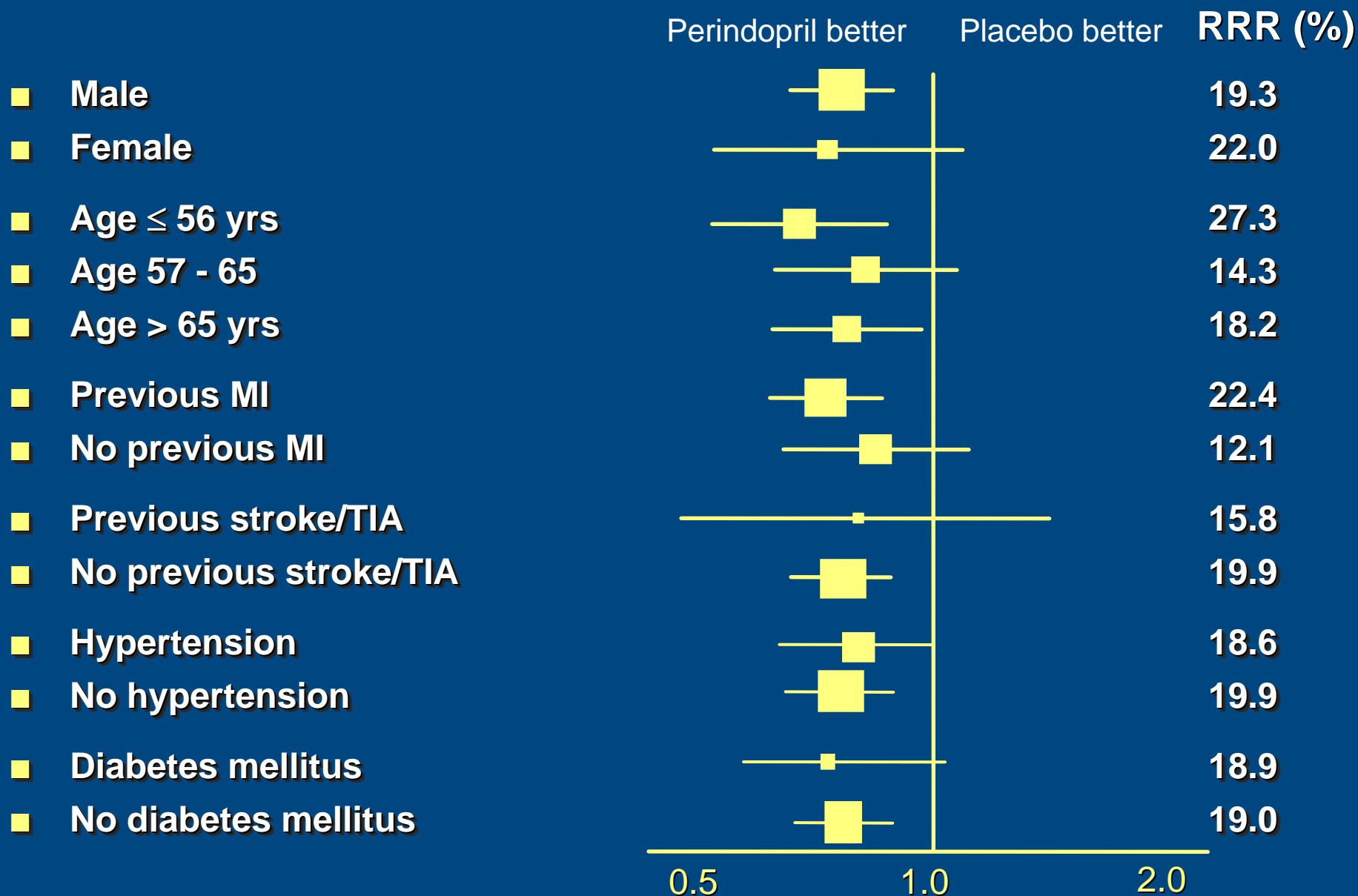
Primary endpoint



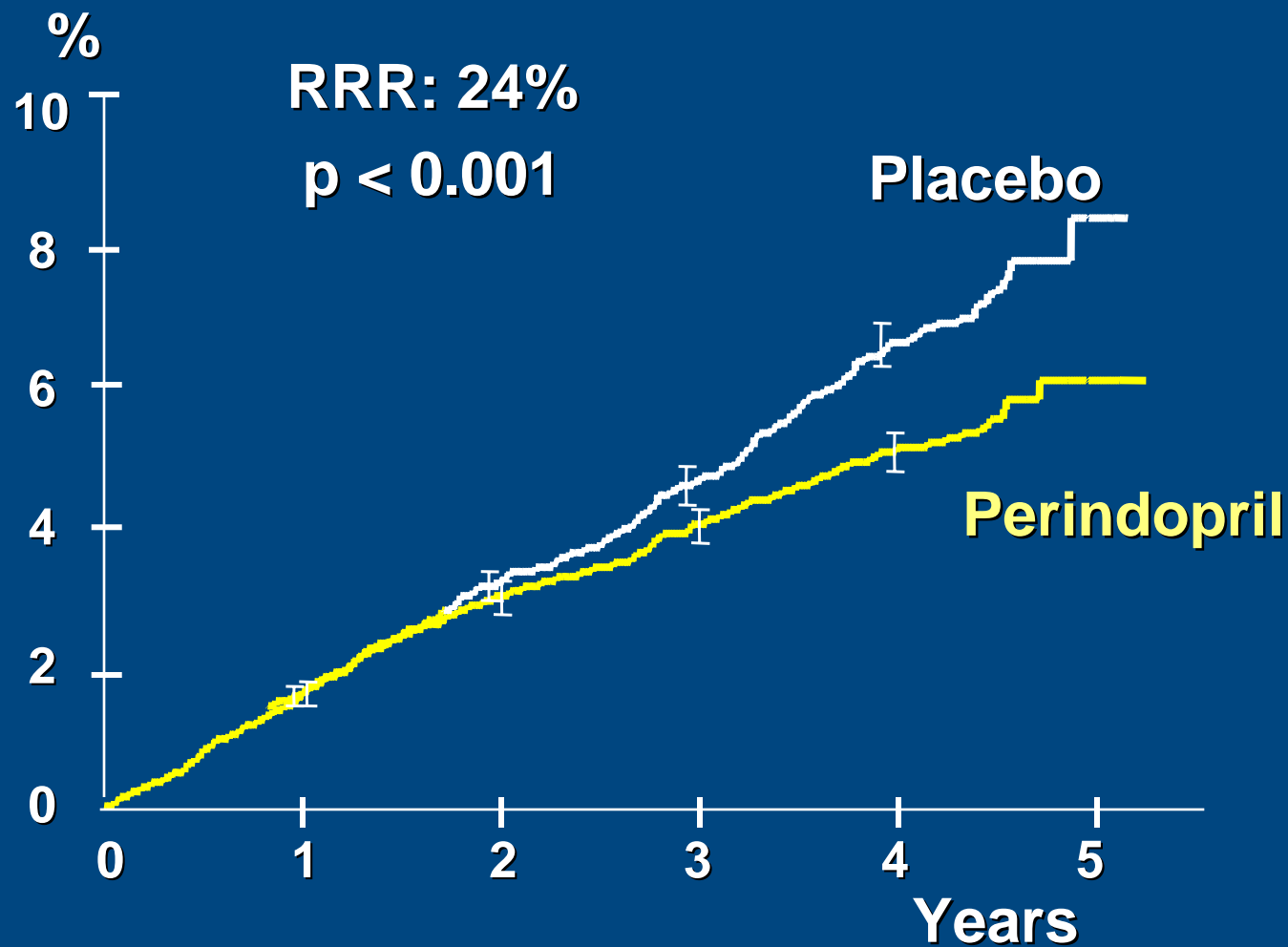
Placebo annual event rate: 2.4%

n = 12 218

Sub-groups analysis



Fatal and non fatal MI



Perindopril 8 mg once a day prevents one cardiovascular death, nonfatal MI or cardiac arrest among every 50 patients with coronary disease treated for 4 years

For a country of 60 million inhabitants, this means that perindopril over a 4 year period will stop 100 000 heart attacks or CV deaths

Summary of results

- **Benefits occurred on top of recommended therapy (*platelet inhibitors, lipid lowering drugs, β -blockers*) and are consistent across predefined sub-groups**
- **Perindopril should be considered for chronic therapy in all patients with coronary disease**

Aim

- To compare the effect of pre-hospital initiation of Tirofiban vs cathlab initiation in patients with acute myocardial infarction who are candidates for primary angioplasty

Methods

Primary End Point:

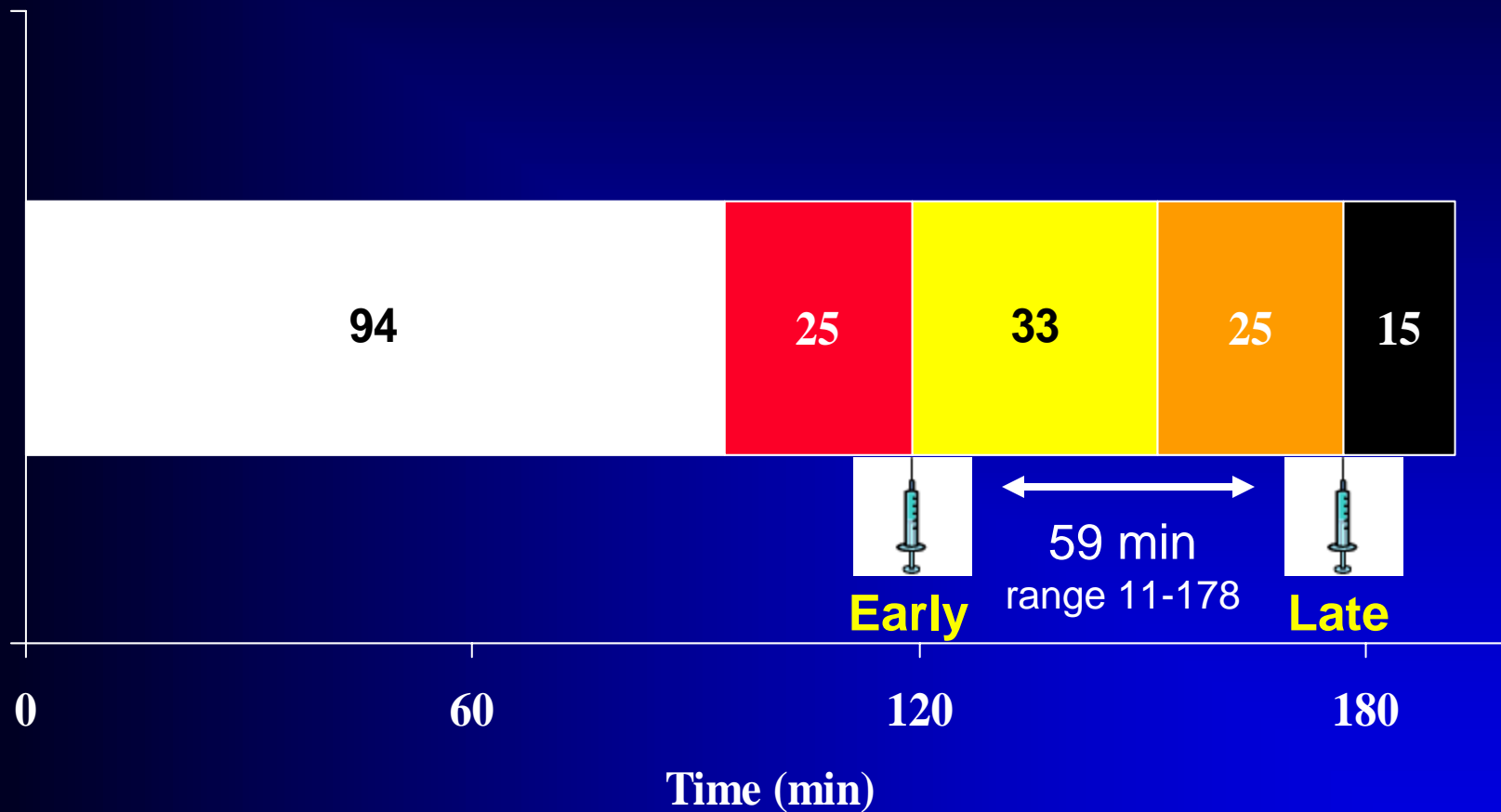
- TIMI 3 flow at initial angiography

Secondary End Point:

- TIMI 0,1,2,3 flow at initial angiography
- Thrombus at initial angiography
- Success PCI

All analyses were performed by an independent core-lab (Diagram, Zwolle, the Netherlands)

Time Delays (minutes)



■ presentation ■ in-outdoor ■ transportation ■ doortoangio ■ angiotoballoon

Data initial angio

	Early (N=243)	Late (N=244)	P
TIMI 3	46 (19%)	36 (15%)	0.22
TIMI 2 or 3	104 (43%)	82 (34%)	0.04
TIMI 0	107 (44%)	143 (59%)	0.0013
TIMI 1	32 (13%)	19 (8%)	
TIMI 2	58 (24%)	46 (19%)	
TIMI 3	46 (19%)	36 (15%)	0.01

Data initial angio

	Early (N=243)	Late (N=244)	P
Thrombus			
Yes	25%	32%	0.06
Fresh occlusion	35%	41%	0.20
Combined*	60%	73%	0.002

* Combined incidence of Thrombus or Fresh Occlusion

Conclusion 1

Facilitation of Primary Angioplasty by

Early initiation of Tirofiban:

- Moderate improvement in Patency
- Significant reduction in Thrombus

Conclusion 2

- In view of the (relative) safety, Tirofiban is attractive for early facilitation of primary angioplasty, on top of aspirin and heparin, in patients with acute myocardial infarction who are transferred to undergo mechanical reperfusion therapy

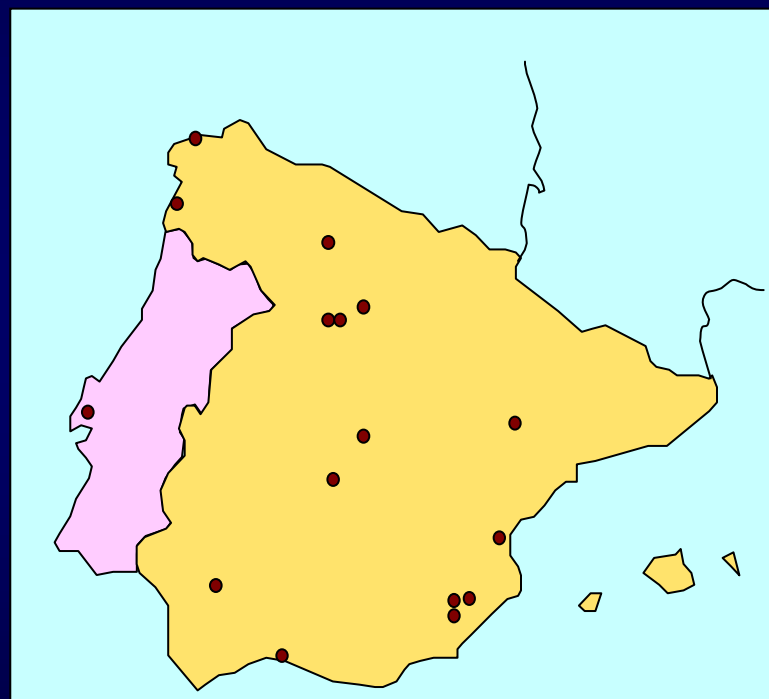


GRACIA – 2 trial

(GRupo de ANálisis de la CArdiopatía ISquémica AGuda)

**Randomised trial
comparing
Primary PCI
versus
Facilitated Intervention
(TNK + Stenting)
in patients with STEAMI**

Francisco F. Avilés
on behalf of the GRACIA investigators



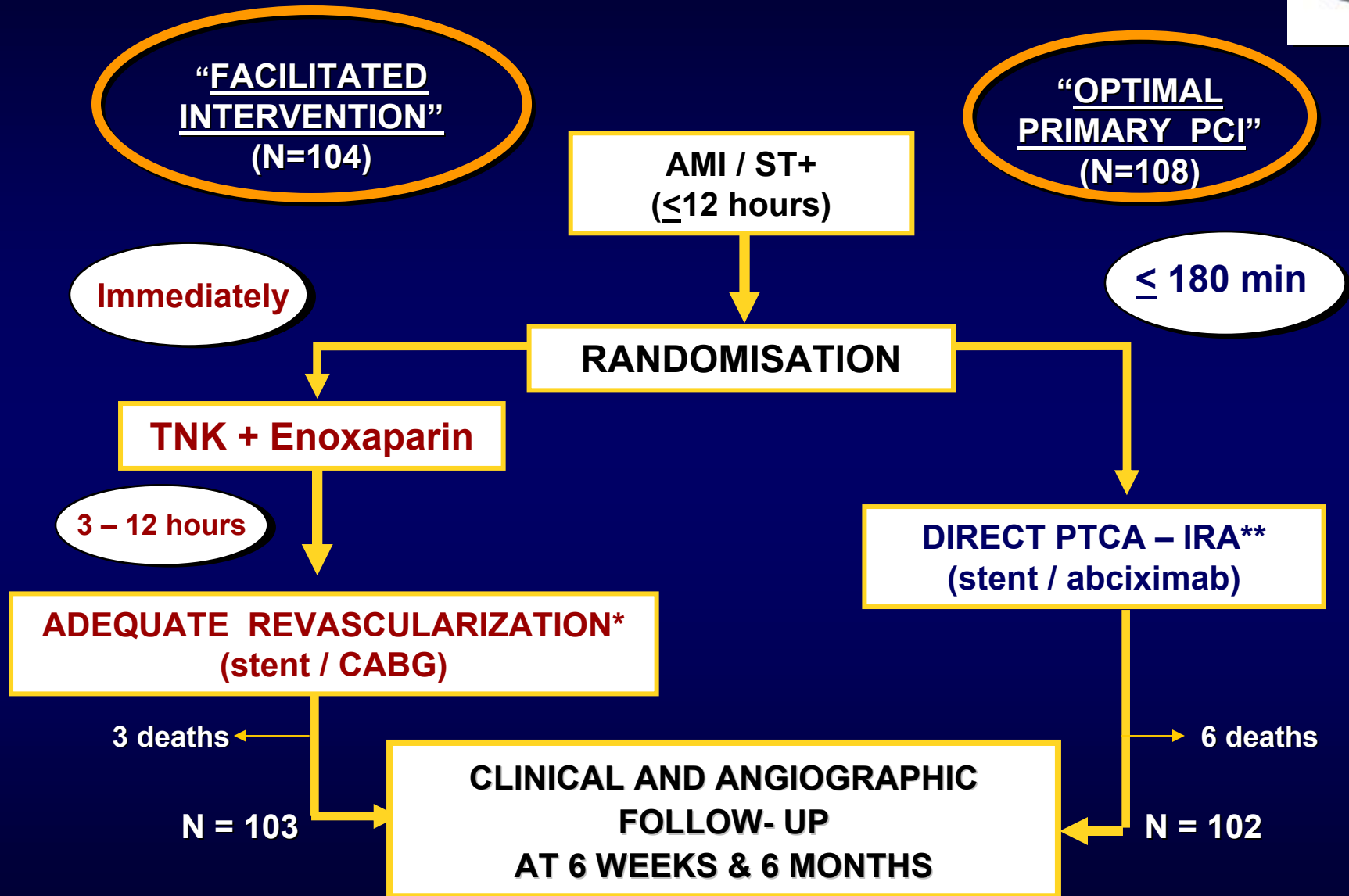
**212 pts
July 2002 – March 2003
15 Centers**

GRACIA – 2

PURPOSE

To compare the safety and efficacy of optimal primary PCI versus a combined reperfusion strategy designed to be widely available

GRACIA-2



(*) Adequate revascularization: revascularization of culprit artery or non-culprit arteries with severe stenosis threatening large areas of myocardium (**) IRA: Infarct Related Artery

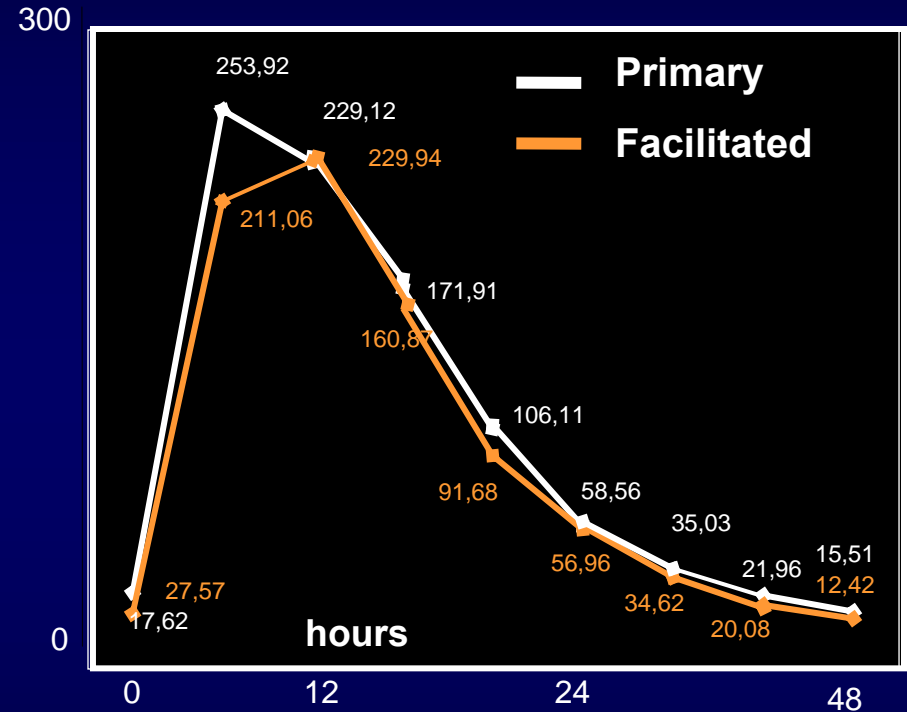
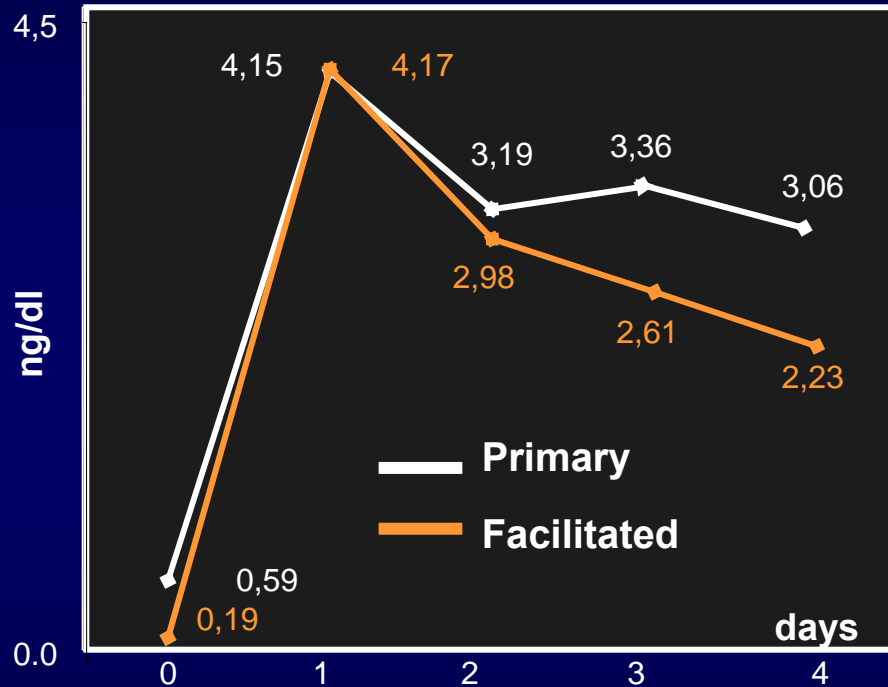
GRACIA – 2

Infarct size



cTnT release

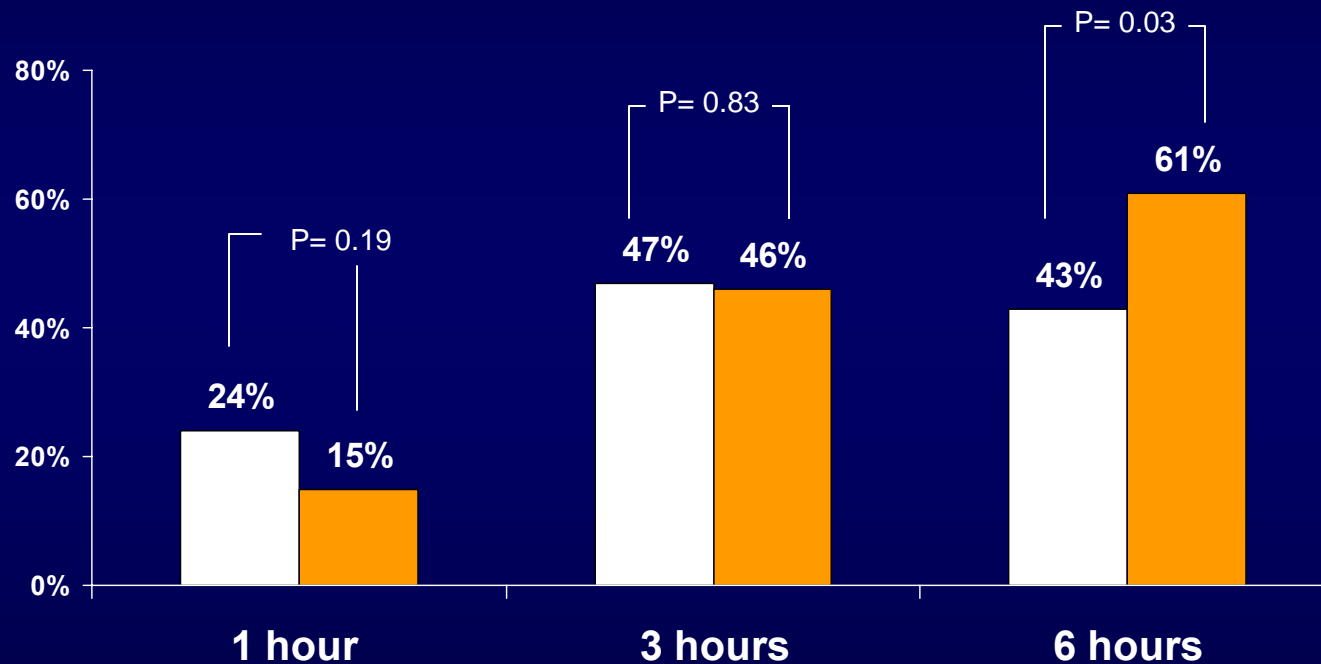
CK-MB mass



Area under the curve	PRIMARY	FACILITATED	p
cTnT	275.5_±211.4	241.8_±155.5	0.52
CK-MB mass	4768.30_±3734.0	4602.01_±3371.2	0.76



ST – segment resolution



Percentage of pts with complete ST normalisation

GRACIA – 2

LV evolution at 6 weeks



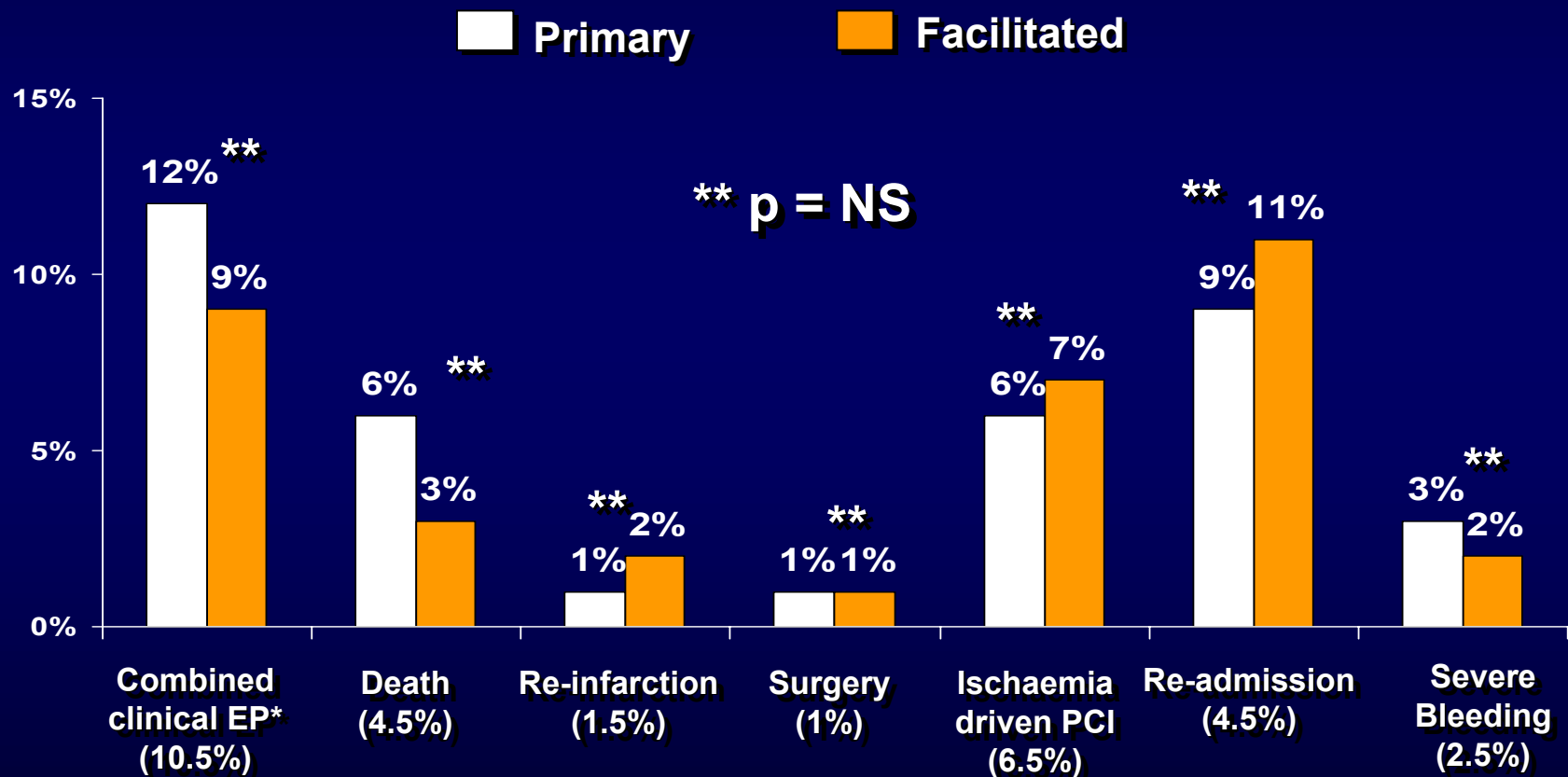
	PRIMARY	FACILITATED	P
LVEF			
Baseline	52.5_±14.3%	53.4_±9.9%	0.7
6-week FU	55.6_±13.4%	56.1_±12.4%	0.9
Δ	3.2_±11.8	3.4_±11.8	0.9
Wall Motion Index			
Baseline	-1.50_±0.4	-1.47_±0.4	0.7
6-week FU	-1.10_±0.6	-1.24_±0.46	0.1
Δ	0.42_±0.67	0.24_±0.50	0.09
EDLV volume index (ml/m²)			
Baseline	126.5_±41	122.01_±47	0.40
6-week FU	139.8_±57.9	129.8_±54.0	0.35
Δ	11.21_±37.76	13.23_±11.8	0.69
ESLV volume index (ml/m²)			
Baseline	56.43_±25.02	57.62_±25.87	0.92
6-week FU	62.32_±35.7	56.23_±31.91	0.35
Δ	5.28_±21.087	-2.07_±28.30	0.16

GRACIA – 2

6-week clinical follow-up



Cardiac events & Severe bleeding



(*) Combined clinical EP: death, nonfatal MI, or ischemia-driven revascularization



CONCLUSIONS

- **Catheterization plus adequate revascularization within 3 – 12 hours of immediate facilitation with TNK seems to be as safe as optimal primary PCI (stent & GP IIb/IIIa inhibitors)**
- **These results suggest that both strategies are similarly effective in restoring myocardial perfusion, preserving left ventricular size & function and benefiting clinical outcome**
- **If this equivalence is confirmed in large studies clinically focused, the proportion of patients with STEAMI who can benefit from early PCI could increase dramatically**

DECOPI

(DEsobstruction COronaire en Post-Infarctus)

**A randomized trial of occluded artery
angioplasty after acute myocardial
infarction**

**P.G.Steg, Hôpital Bichat, Paris, France
for the DECOPI Study Group**

DECOPI

First Q-wave acute myocardial infarction

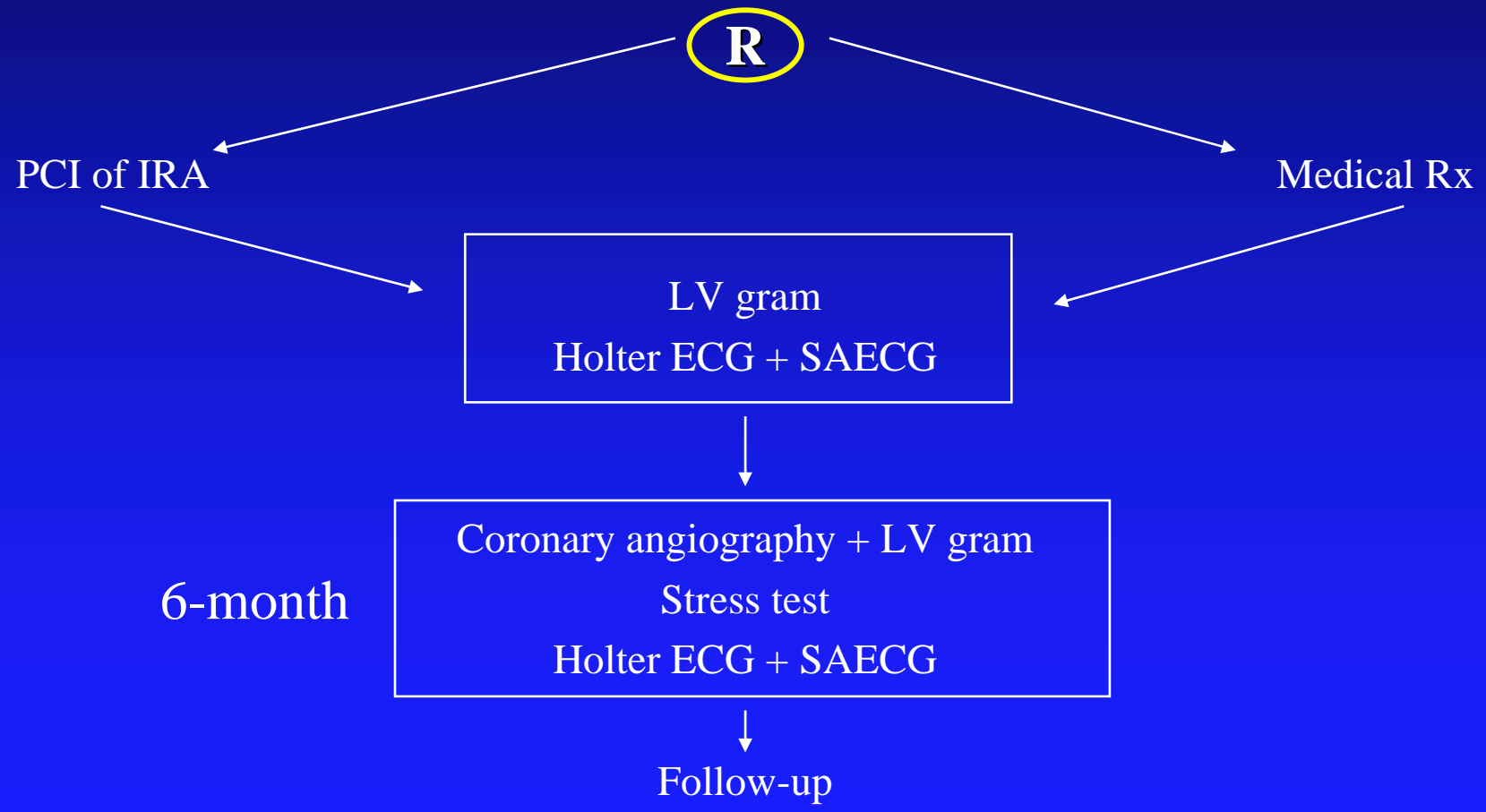
Age 20 to 75 years

No spontaneous or low-level recurrence of ischemia

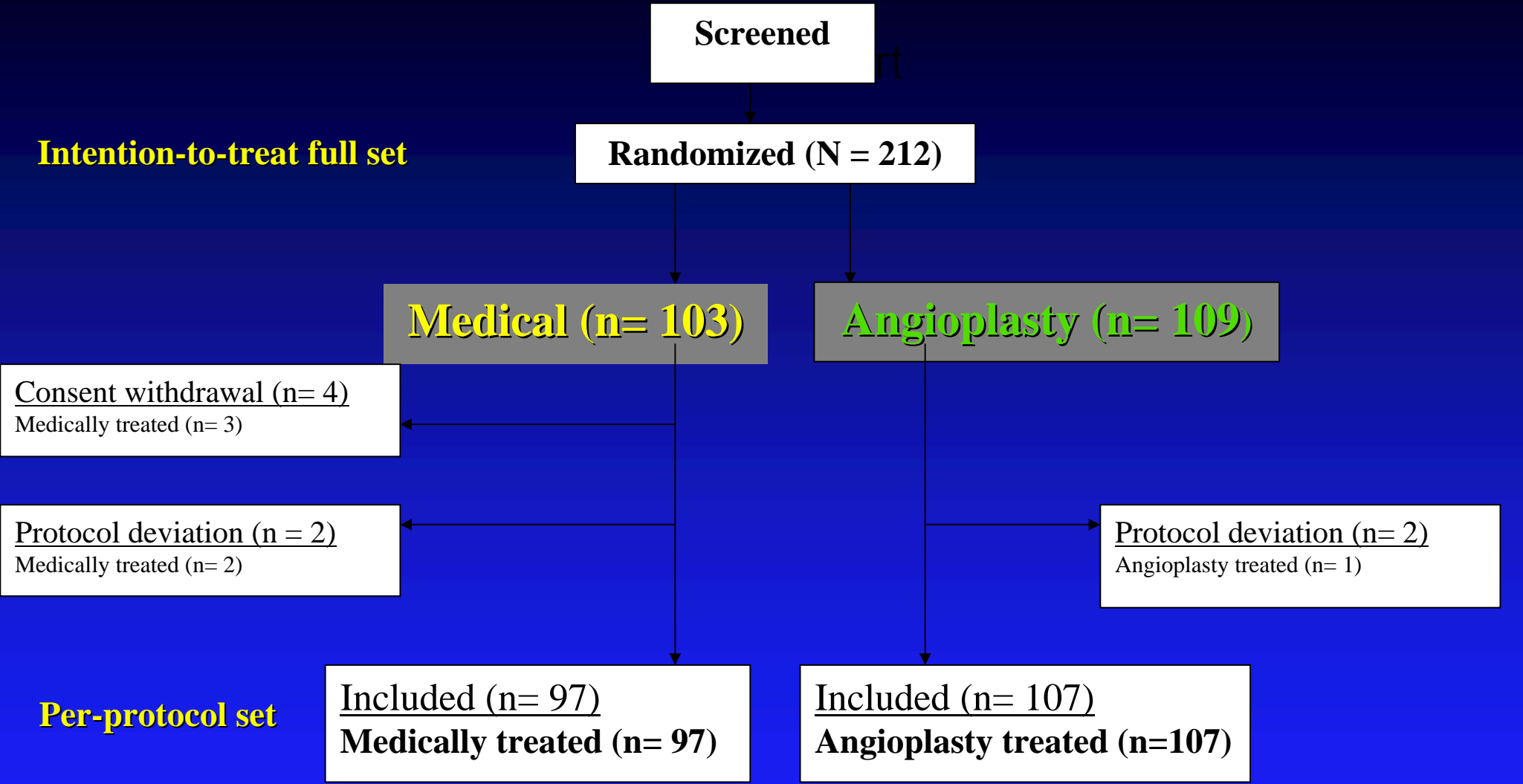
TIMI 0-1 flow in infarct-related artery at Days 2 to 15

Infarct vessel size > 2,0 mm by QCA

Informed consent



DECOPI



Primary endpoint

	Medical n = 103	PCI n = 109	HR [95%CI]	p
Mean Follow-up (months)	33.2	35.7		
CV deaths	6.8%	5.5%	0.765 [0.255-2.295]	0.63
Non-fatal MI	1.9%	2.7%	1.414 [0.236-8.464]	0.70
Non-fatal VT/VF	0	0	—	—
Primary endpoint	8.7%	7.3%	0.80 [0.307-2.06]	0.64

Secondary endpoints

	Medical n = 103	PCI n = 109	HR or mean difference [95%CI]	p
Admissions for CHF	4.8%	2.7%	0.54 [0.13-2.27]	0.40
Primary endpoint + admissions for CHF	12.6%	10.1%	0.787 [0.352-1.756]	0.56
6-month LVEF (core)	40.0%	43.5%	5.54 [1.18-9.90]	0.025
6-month IRA patency	39.7%	82.7%		<0.0001

6-month patency and outcomes

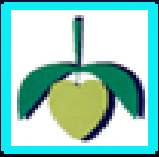
N(%) Median [Q1-Q3]	Occluded IRA	Patent IRA	HR [95% CI]	P
LV EF (%)	53 [43.5-60]	59 [49-57]	5.5 [1.5-9.5]	0.004
All cause mortality	9.1%	1%	0.099 [0.012-0.82]	0.032
CV death	6.1%	0%	—	0.01*
Primary endpoint	6.1%	2%	0.32 [0.058-1.72]	0.18

*:Gray test

Coronary artery bypass surgery
versus stenting for the treatment
of multi-vessel disease
ARTS-1, SoS, ERACI-2 and
MASS-2 meta-analysis

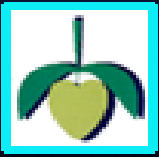
Marcus D. Flather
Nestor Mercado, Eric Boersma
on behalf of the Trial Investigators

August 31, 2003
ESC Vienna



Background

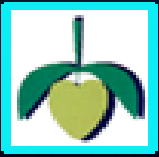
- Meta analysis of randomized trials of PTCA (without stents) vs CABG show lower death/MI rate with CABG
- High rates of repeat revascularisation in PTCA group
- Many trials in single vessel disease
- Use of stents may improve outcomes for percutaneous revascularisation



Methods

- Search for randomized trials of PCI with stent compared to coronary artery surgery in patients with multi-vessel coronary disease
- Identify key baseline, treatment and outcome variables
- Obtain data for individual patients in each trial from the trial investigators
- Perform analyses using pooled data
- Standard statistical methods for a meta-analysis

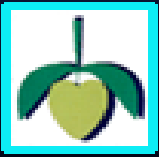
Stent vs. surgery meta analysis



Main outcome measures

- Primary outcome measure: combined rate of death, non-fatal MI or stroke at one year
- Secondary outcomes:
 - death at one year
 - rate of repeat revascularisation at one year
 - Composite MACCE (death, MI, stroke, repeat revascularisation at one year)

Stent vs. surgery meta analysis



Results 1

- 5 Trials identified: ARTS-1, SoS, ERACI-2, MASS-2 and AWESOME
- AWESOME excluded as patients were very high risk (different to other studies)
- MASS-2 medical treatment arm excluded
- From 1995 to 2000, 3051 patients enrolled in 113 participating centres
- 1518 allocated to PCI with multiple stent implantation and 1533 to CABG

Stent vs. surgery meta analysis



Results 2

- Mean time from randomisation to treatment was 15 ± 22 days for PCI group and 20 ± 29 days for CABG group
 - 98% of PCI group and 96% of CABG group received the assigned treatment
 - In PCI group, mean (\pm SD) 2.4 ± 1.1 lesions were successfully revascularised, (79% with stent)
 - 6.7% (102) received GP IIb/IIIa inhibitors
 - In CABG group, mean of 2.7 ± 0.8 anastomoses were performed (90% received at least one arterial conduit)
 - Complete revascularisation achieved in 82% of the patients in the CABG group as compared to 54% in PCI ($P < 0.001$)
- Stent vs. surgery meta analysis*

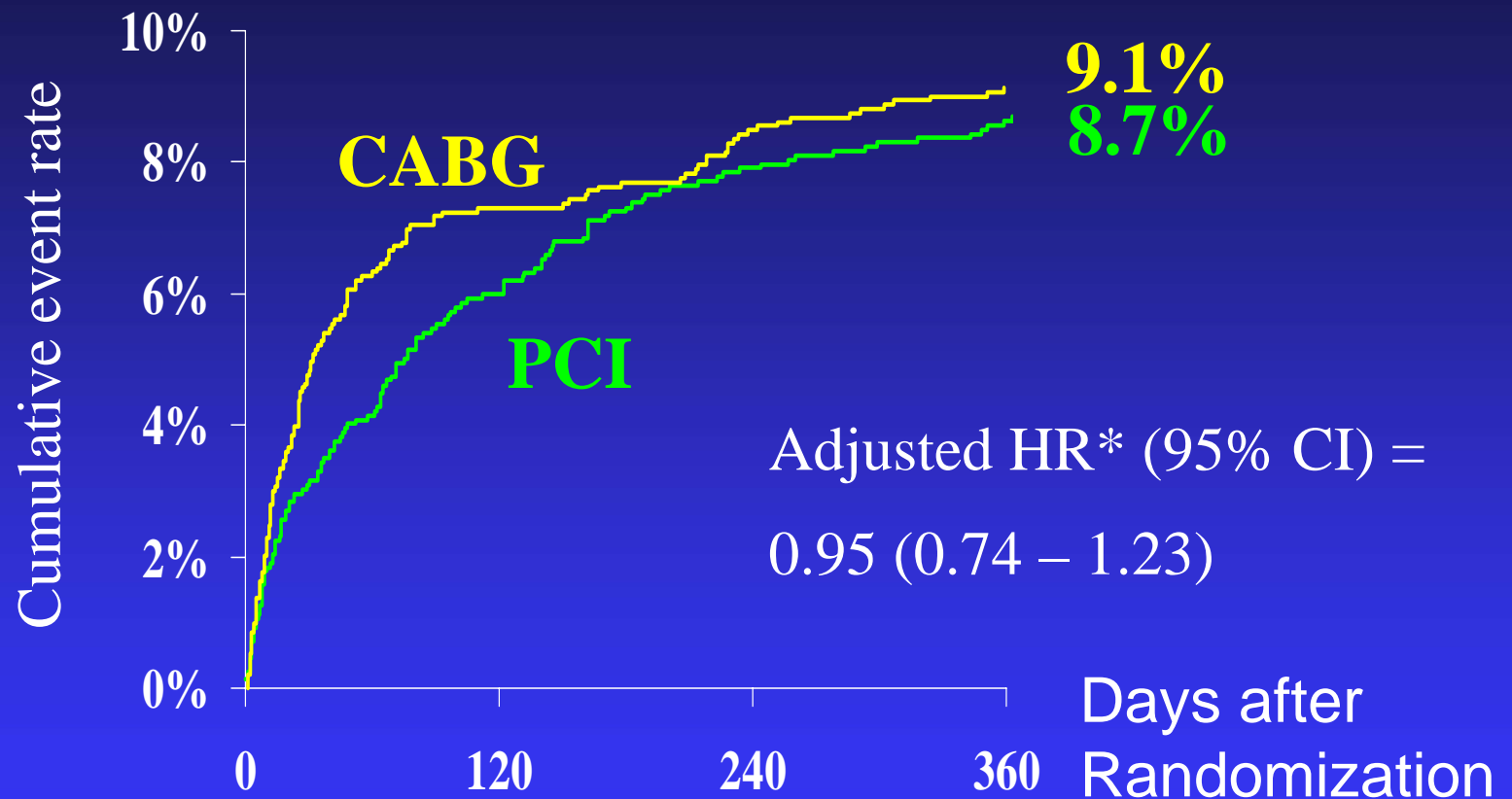


Baseline characteristics

Stent vs. surgery meta analysis



Death, non-fatal myocardial infarction and stroke at one year



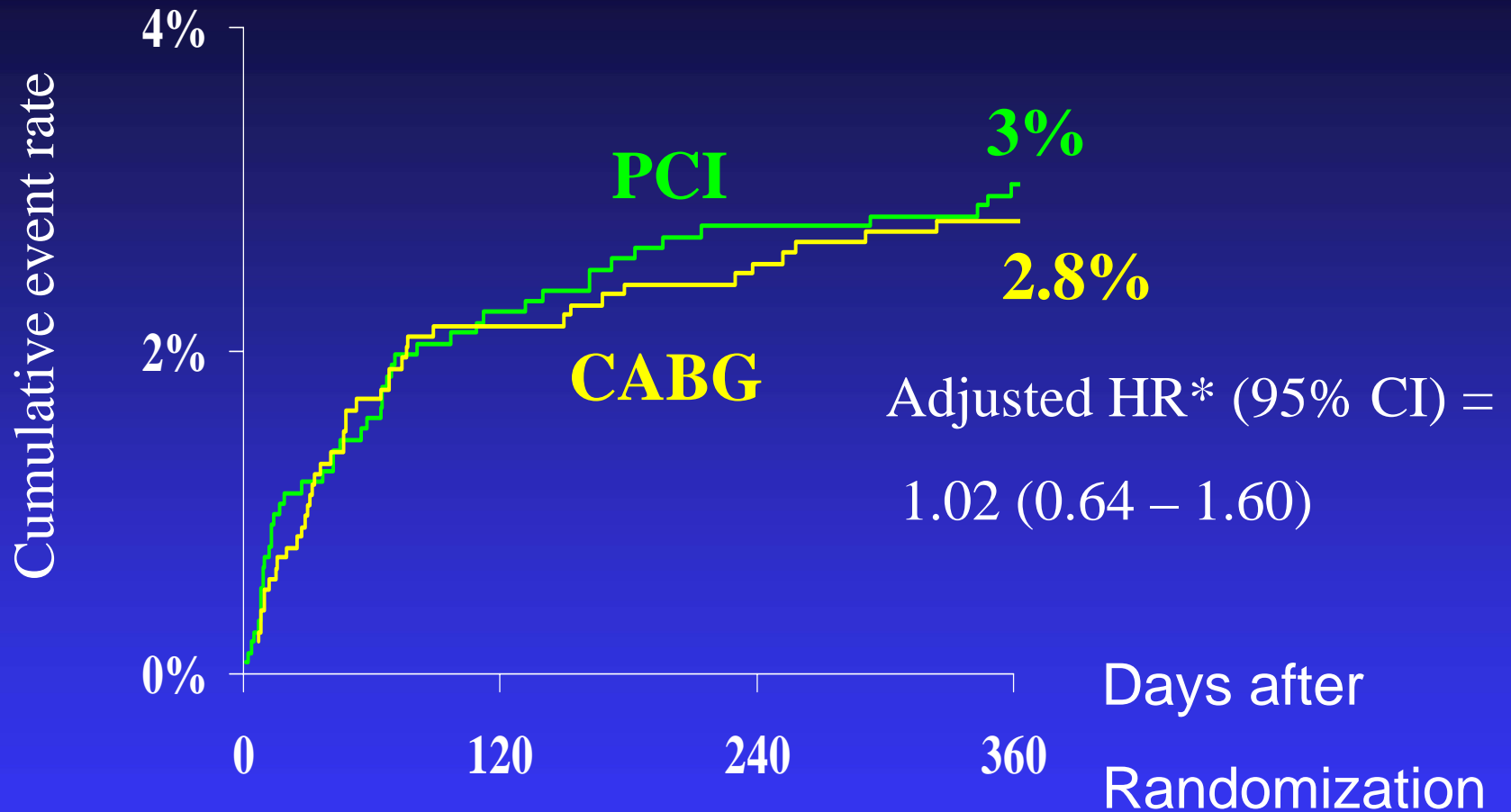
Numbers at risk

PCI	1518	1427	1398	1387
CABG	1533	1422	1404	1393

Stent vs. surgery meta analysis



All cause mortality at one year



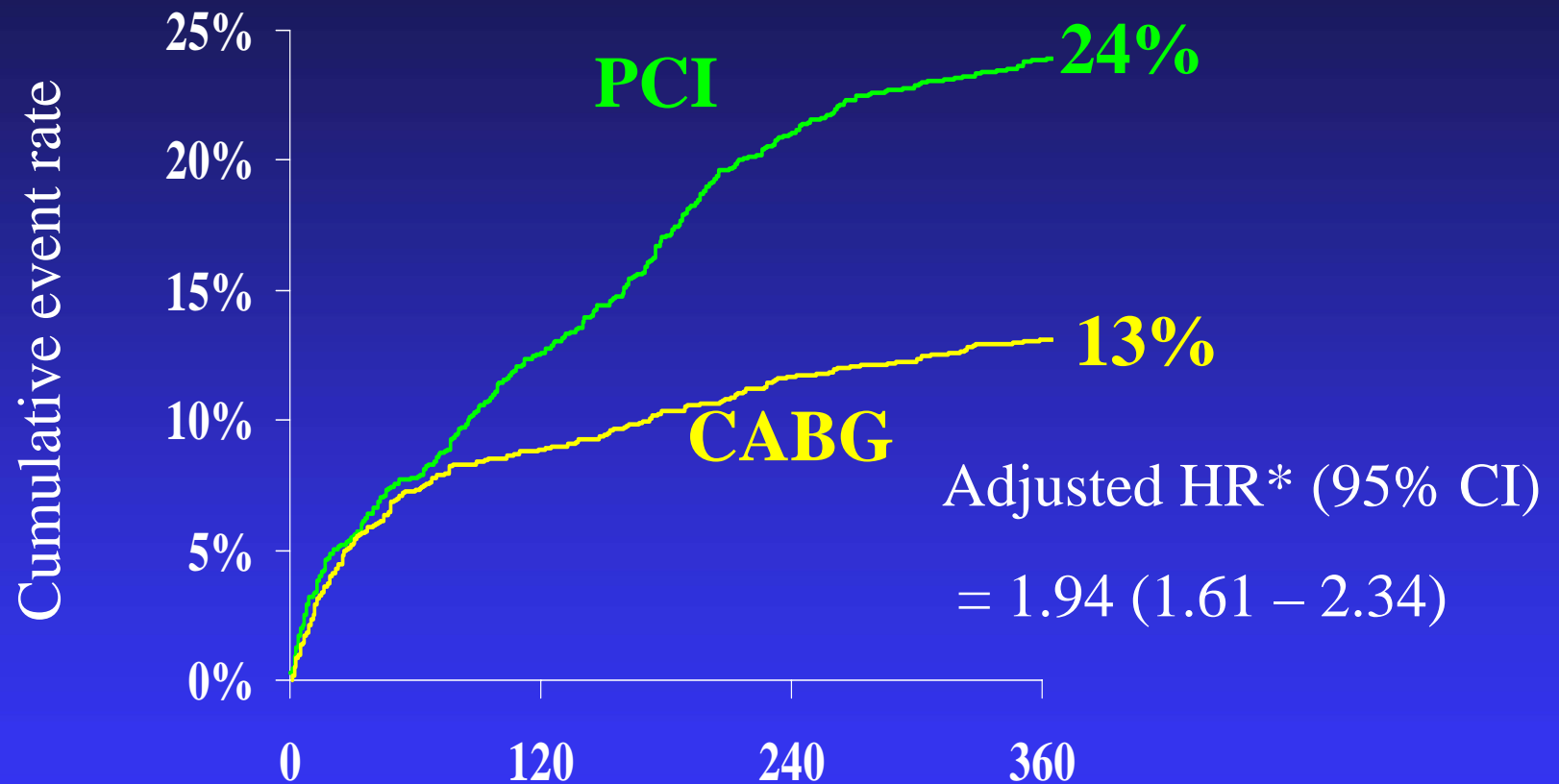
Numbers at risk

PCI	1518	1484	1476	1472
CABG	1533	1501	1495	1490

Stent vs. surgery meta analysis



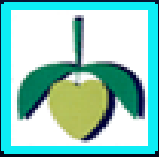
Composite MACCE: Death, non-fatal myocardial infarction, stroke and repeat revascularization procedures



Numbers at risk

PCI	1518	1327	1198	1156
CABG	1533	1397	1354	1332

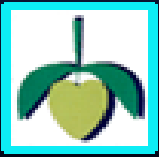
Stent vs. surgery meta analysis



Results (*Continued*)

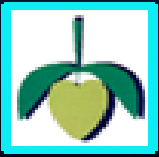
- Repeat revascularisation occurred in 18% in PCI group compared to 4.4% in CABG group (Adjusted HR=4.42 [95%CI 3.33-5.87], $p < 0.0001$)
- CCS angina class 0 (i.e. no angina): CABG 82% compared to PCI 77% $p = 0.001$)
- Significant heterogeneity for primary outcome in meta analysis driven largely by ERACI and MASS
- No major subgroup interactions were found: in diabetics mortality was 5.6% in the PCI group versus 3.5% in CABG group (HR=1.61 [95%CI 0.72-3.61], $p = 0.245$).

Stent vs. surgery meta analysis



Limitations

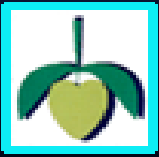
- In spite of pooling, sample size of 3051 is quite small
- Patients enrolled appear to be highly selected and represent low to average risk for CABG
- Studies are all “open” and therefore repeat revascularisation may not be a valid outcome as it is driven in part by knowledge of the index procedure
- Definitions of MI varied from study to study



Conclusions and Discussion

- For low to average risk patients PCI appears to offer a similar clinical outcome to CABG
- Rates of repeat revasc still about 4 times higher in PCI group (although lower than pre-stent era)
- More randomized studies of PCI vs CABG still needed to assess role of drug eluting stents and role of multi-vessel PCI in higher risk patients

Stent vs. surgery meta analysis

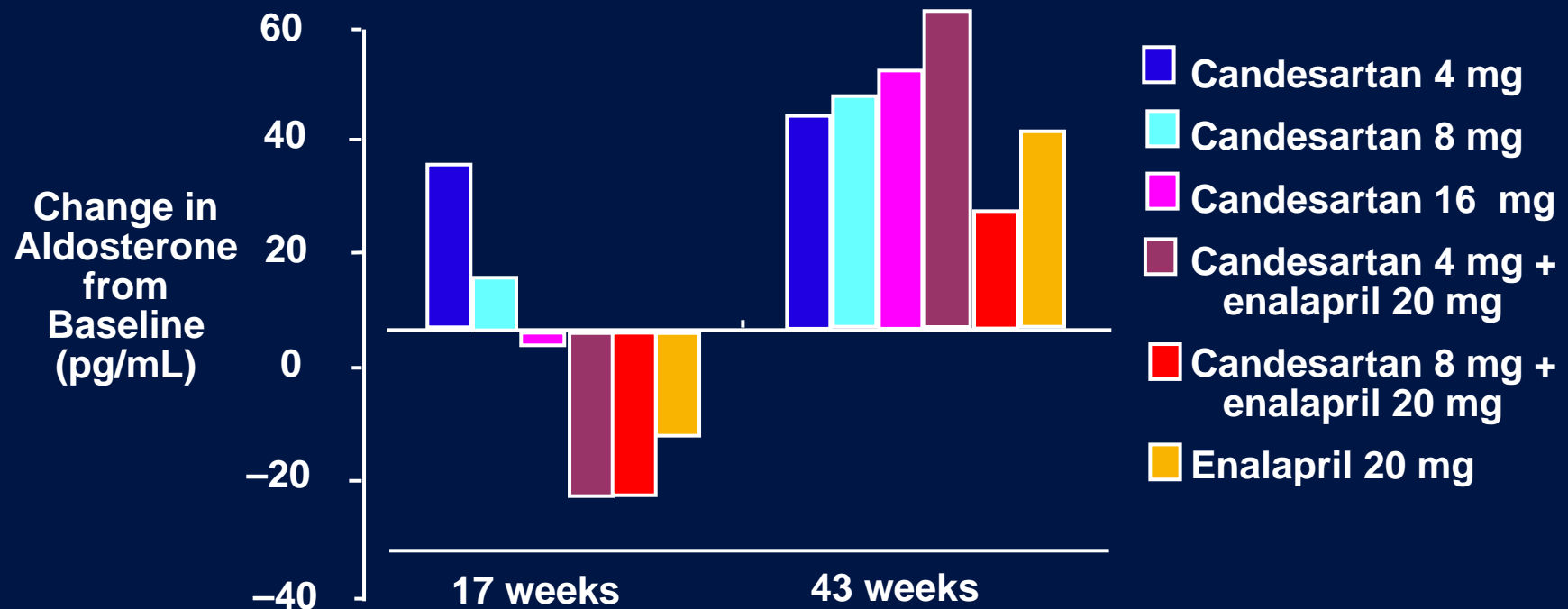


Acknowledgements

- Principal Investigators: William Wijns, Patrick W. Serruys, Ulrich Sigwart, MD, Rodney H. Stables, William W. O'Neill, Alfredo Rodriguez, Pedro A. Lemos, Whady A. Hueb, Bernard J. Gersh, Jean Booth
- All the Trial Investigators
- Supporting companies and funding sources (*to be added*)
- Clinical Epidemiology Unit, Thoraxcenter, Rotterdam

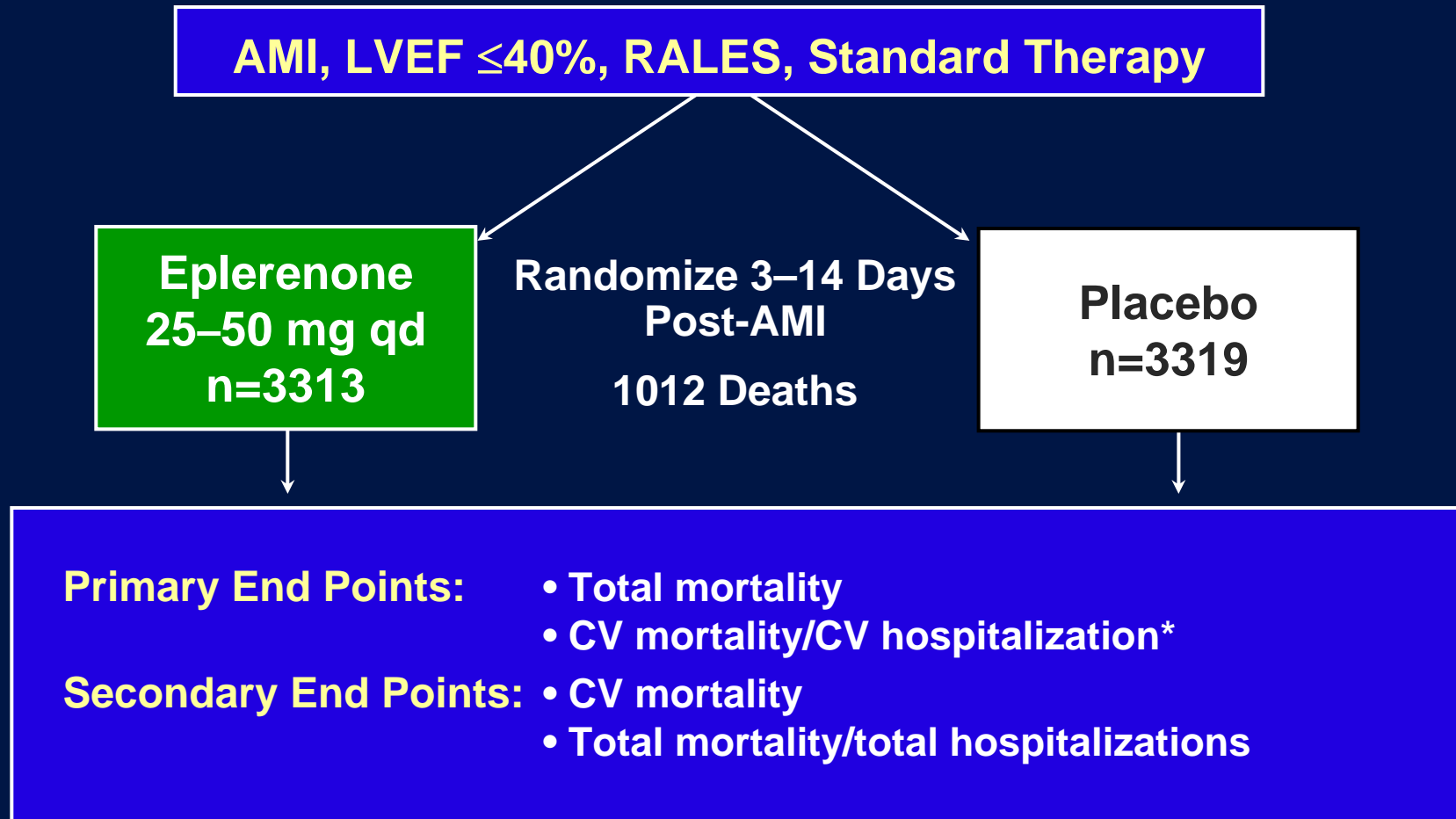
Stent vs. surgery meta analysis

Aldosterone “Escape” Despite Angiotensin II Blockade



RESOLVD Investigators. American College of Cardiology. 1998.

EPHESUS: Design

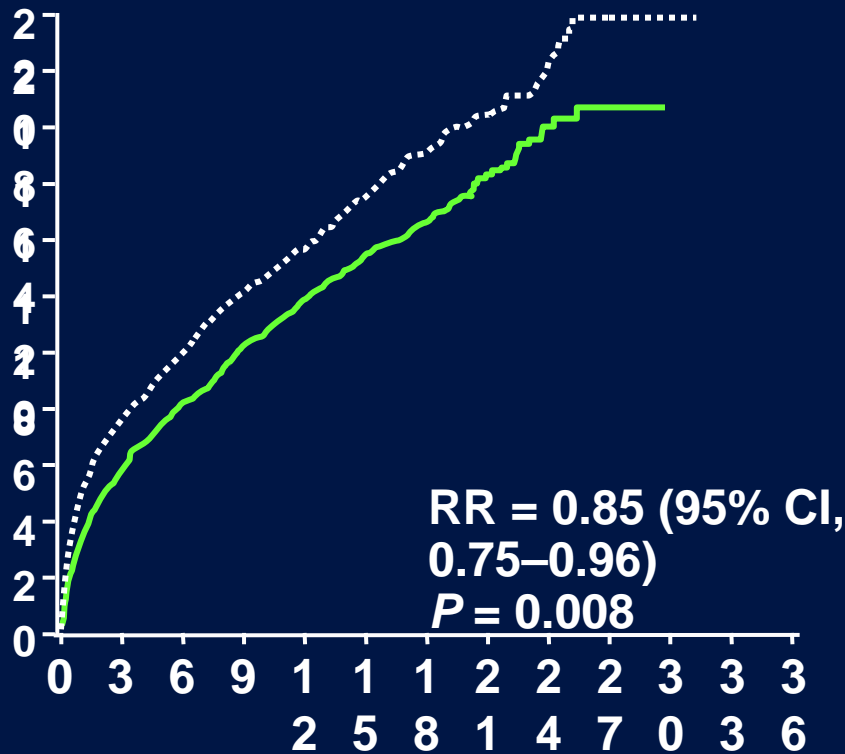


LVEF = left ventricular ejection fraction.

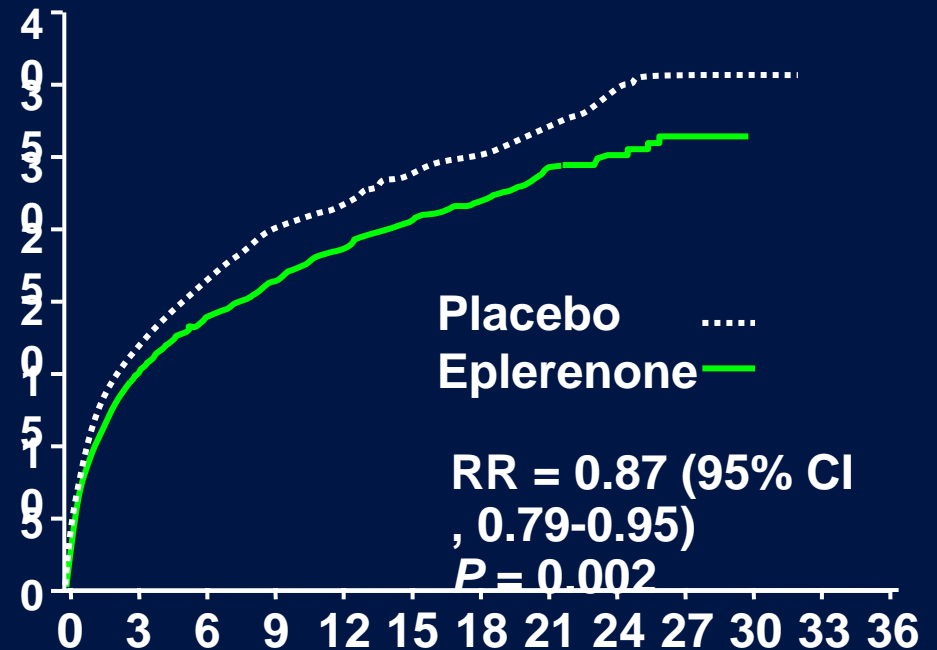
*CV hospitalization = hospitalization for HF, MI, stroke, or ventricular arrhythmia.

EPHESUS MAIN RESULTS

Total Mortality
NNT 50



CV Mortality+ CV Hosp
NNT 33



Subgroup Analysis of Total Mortality by Baseline ACEI/BB Treatment

Overall EPHESUS Population

No ACEI, No BB

(EPL n=33, 21.4%; PBO n=34, 20.0%)

No ACEI, BB

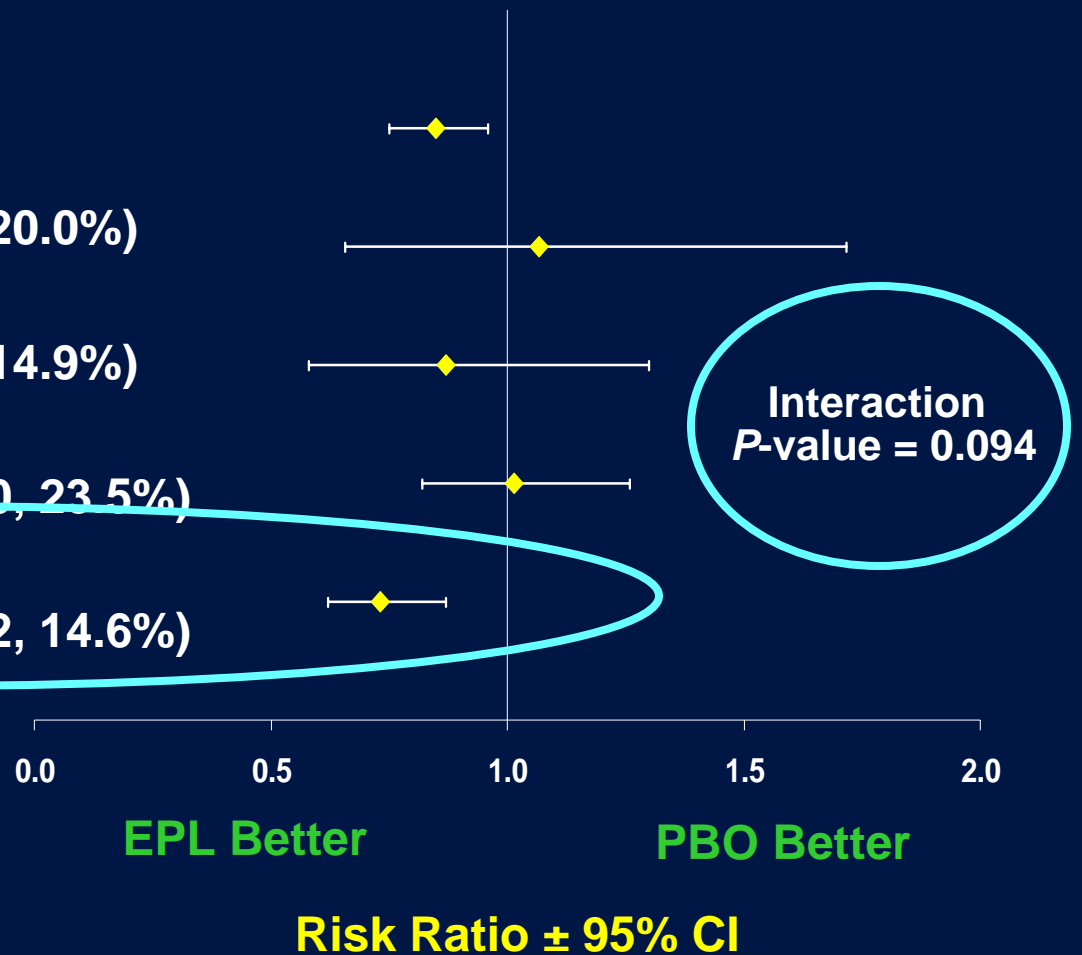
(EPL n=48, 13.0%; PBO n=48, 14.9%)

ACEI, No BB

(EPL n=168, 24.3%; PBO n=160, 23.5%)

ACEI, BB

(EPL n=229, 10.9%; PBO n=312, 14.6%)



Subgroup Analysis of CV Mortality/ Hospitalization by Baseline ACEI/BB Treatment

Overall EPHESUS Population

No ACEI, No BB

(EPL n=46, 29.9%; PBO n=58, 34.1%)

No ACEI, BB

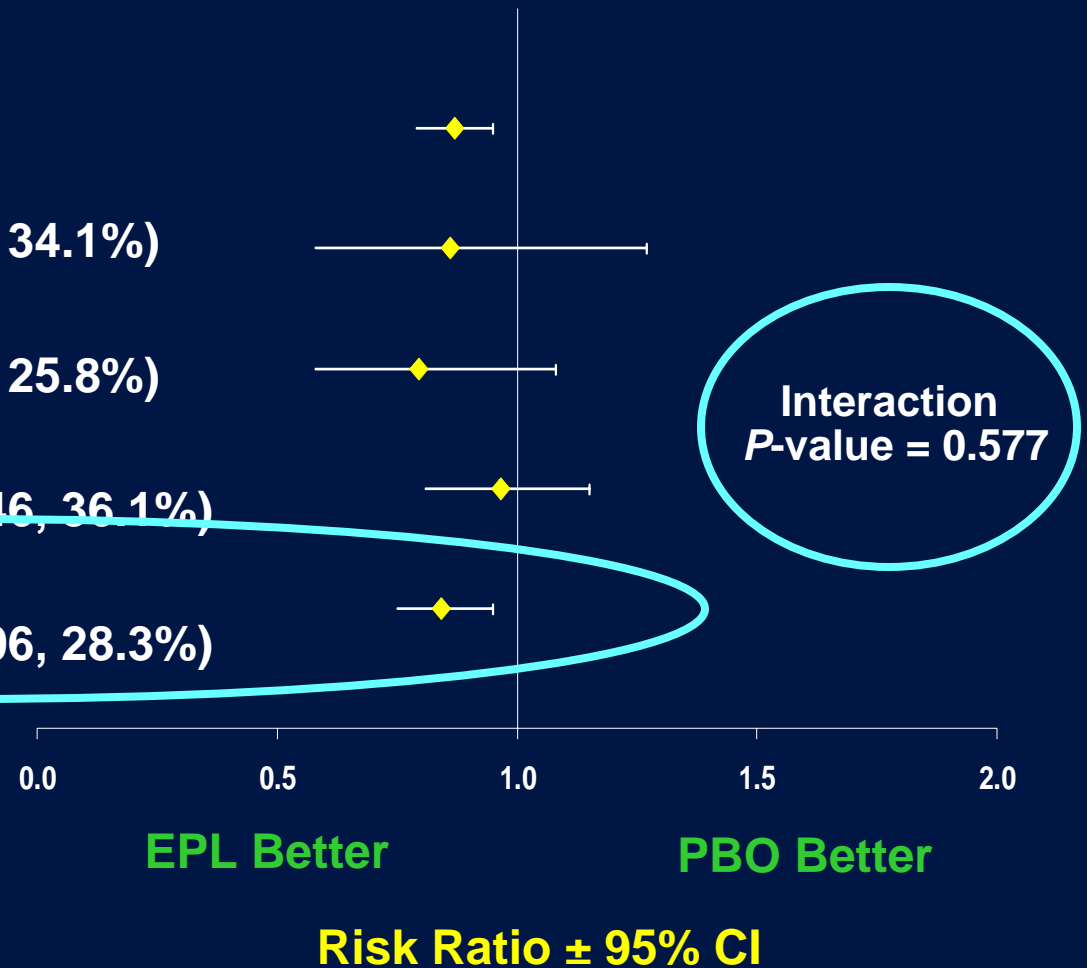
(EPL n=77, 20.8%; PBO n=83, 25.8%)

ACEI, No BB

(EPL n=245, 35.4%; PBO n=246, 36.1%)

ACEI, BB

(EPL n=517, 24.6%; PBO n=606, 28.3%)



Conclusion

Results of Retrospective Analysis

- Unlike VAL-HeFT, EPHEBUS demonstrates a preserved treatment effect in patients on baseline ACEI/BB therapy.
- Initiation or discontinuation of ACEI/BB therapy during the trial does not appear to impact EPL treatment benefit.

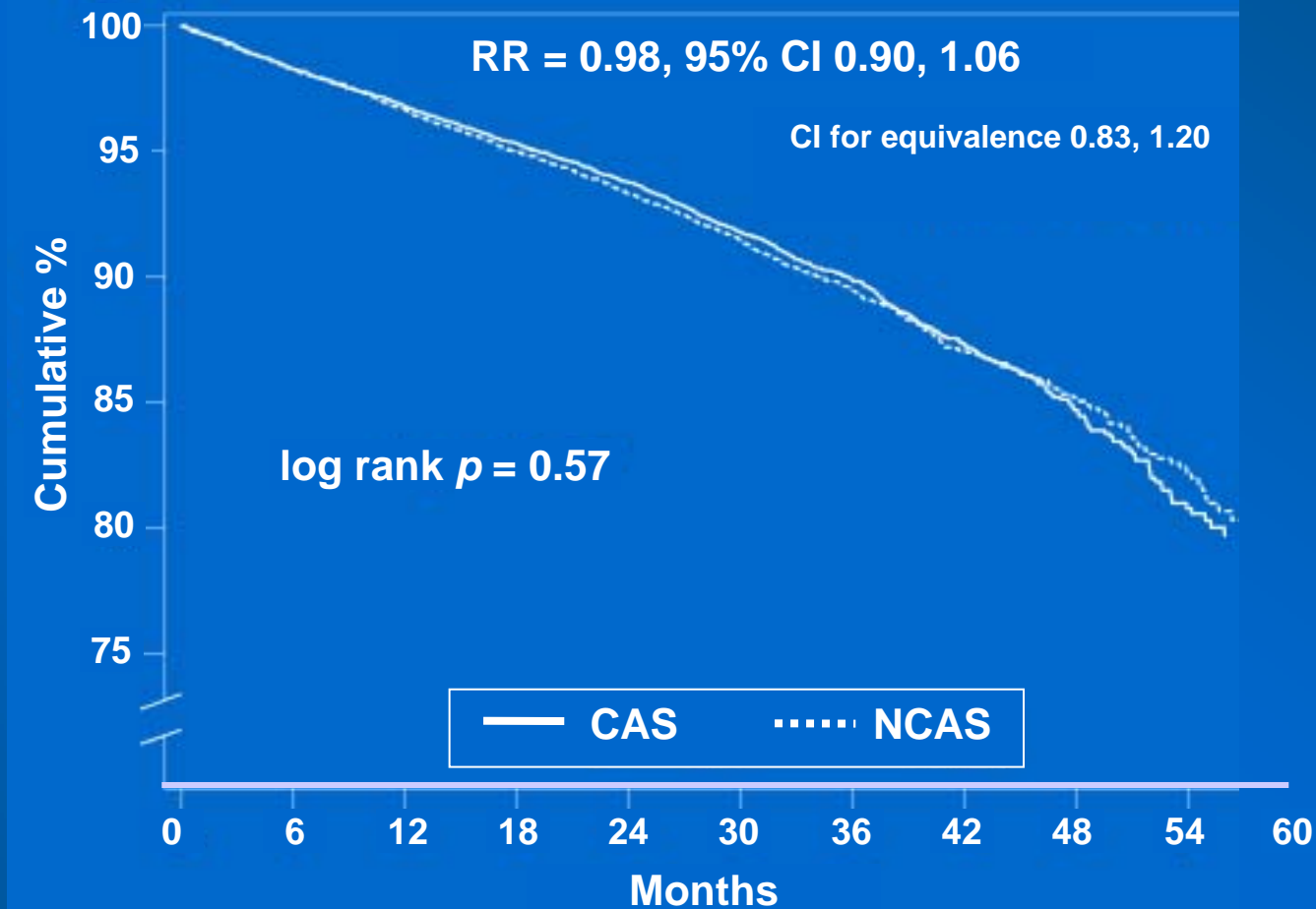
INVEST

- Design
 - Prospective, randomized, open trial with blinded endpoint evaluation (PROBE) to assess outcomes (death, MI, stroke) in hypertensive CAD patients treated with either a calcium antagonist based (**verapamil SR**) or noncalcium antagonist based (**atenolol**) treatment strategy
- Hypothesis
 - Treatment strategies are equivalent (**CI 0.83,1.20**)
- BP Goals
 - According to JNC VI (< 130/<85 mmHg for pts with diabetes and renal dysfunction, <140/<90 mmHg for all others)
- Study Characteristics
 - Conducted in 862 Sites in 14 Countries
 - Recruitment from 9/97-12/00; 22,576 patients randomized (ITT)
 - Follow-up completed end of 2/03
 - Preliminary results 4/2/03; updated results 9/3/03



Alive, Free of MI or Stroke

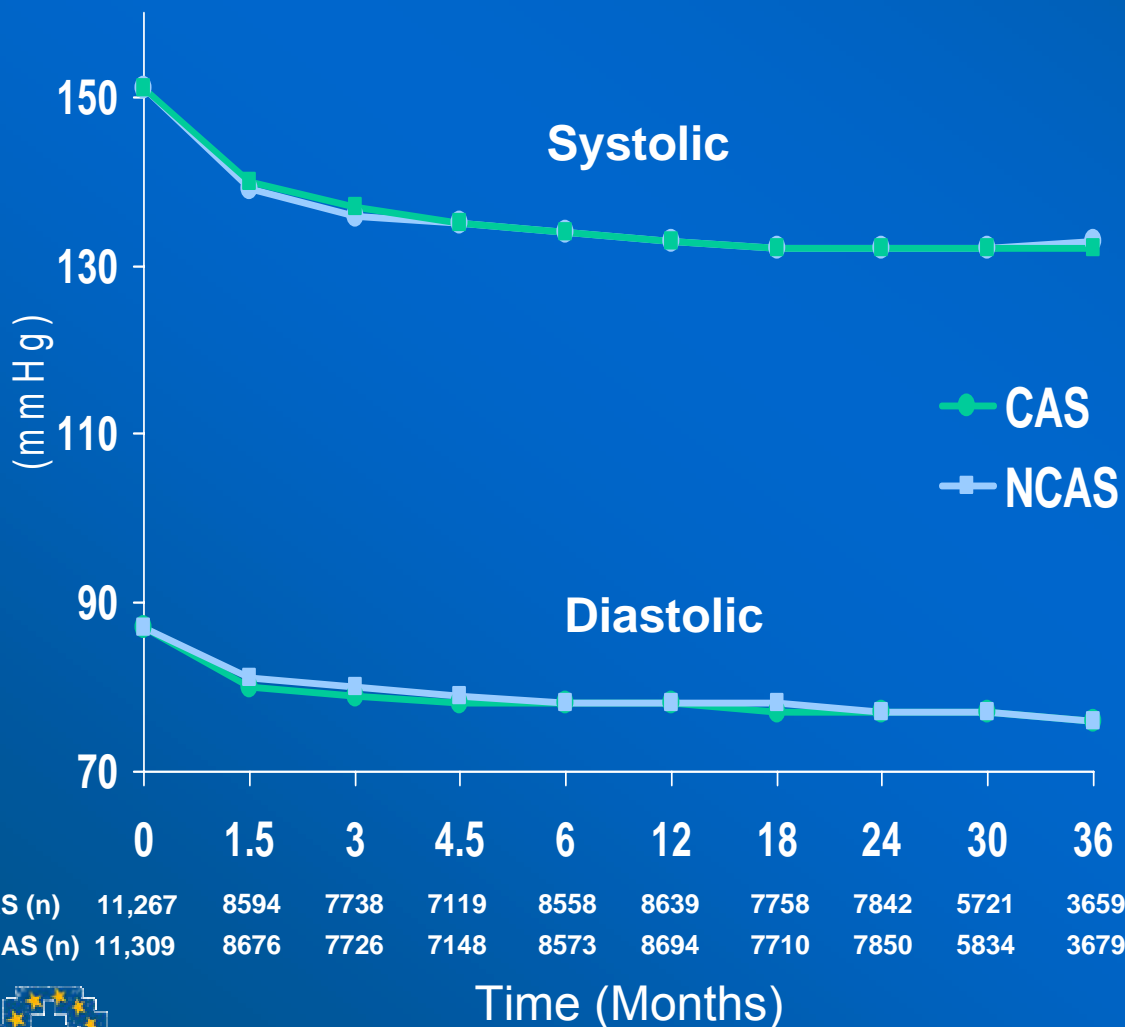
Primary Outcome



- Total follow-up 61,835 patient-yrs
- Mean follow-up 2.7 yrs/patient
- Annual event rate = 3.6%

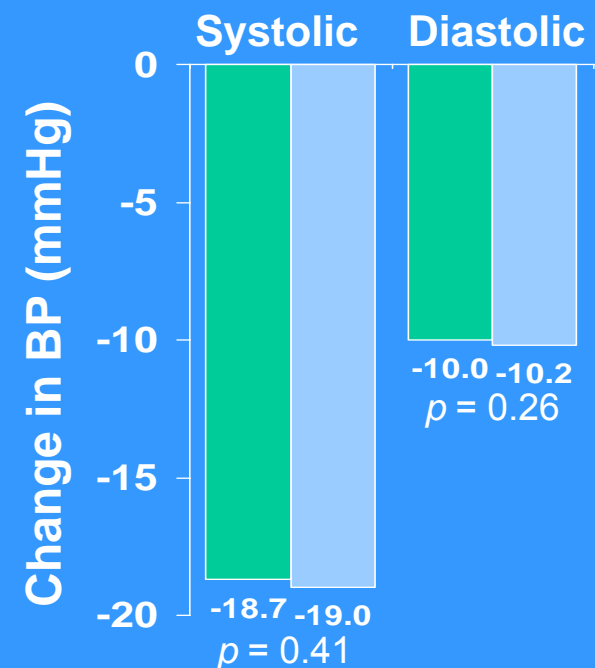


Mean Blood Pressure



CAS (n)	11,267	8594	7738	7119	8558	8639	7758	7842	5721	3659
NCAS (n)	11,309	8676	7726	7148	8573	8694	7710	7850	5834	3679

24 Months



Outcomes in Patients Without Diabetes at Baseline

Unadjusted Relative Risk with 95% CI

Outcome	CAS n=8101 No. (%)	NCAS n=8082 No. (%)	
New-Onset Diabetes	569 (7.03)	665 (8.23)	
Death or New-Onset Diabetes	1050 (12.97)	1177 (14.57)	
Primary Event or New Onset Diabetes	1185 (14.63)	1313 (16.25)	

0.80 1.0 1.2
CAS Better NCAS Better

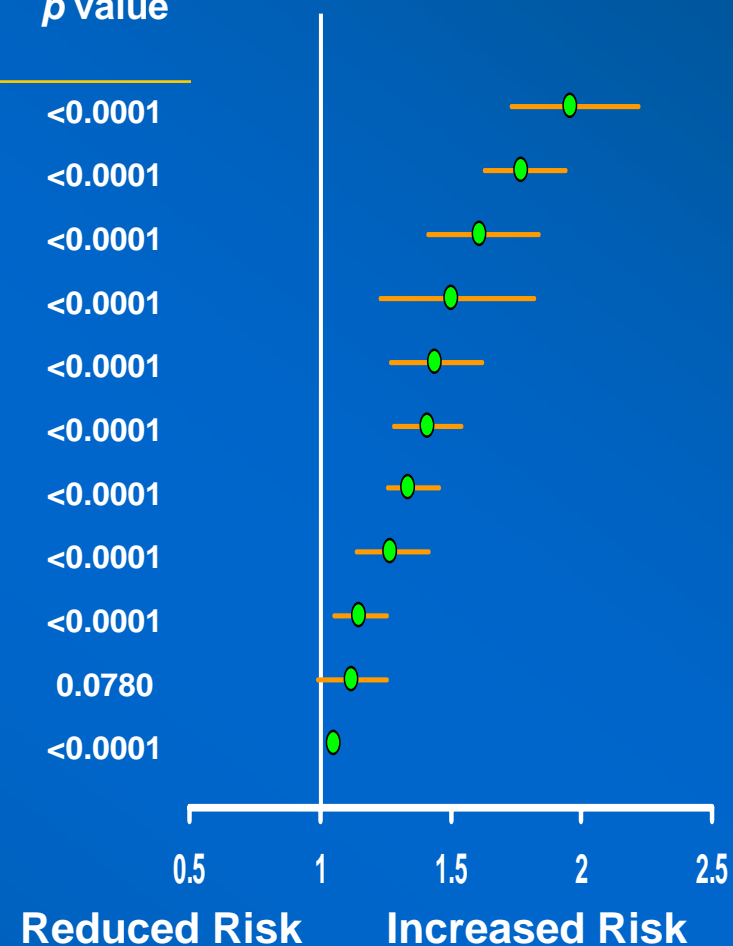
n= patients without diabetes at baseline



Factors Associated With Increased Risk For The Primary Outcome

Hazard Ratio Estimates From Multivariate Stepwise Model

Factor	No./Total	Event Rate	p value
CHF (Class I, II, III)	302/1256	24%	<0.0001
Diabetes	913/6400	14%	<0.0001
US Resident	1999/17131	12%	<0.0001
Renal Insufficiency (Cr \leq 4)	114/424	27%	<0.0001
Stroke/TIA (<1 Month)	322/1629	20%	<0.0001
Smoker	1242/10454	12%	<0.0001
MI (<1 Month)	1012/7218	14%	<0.0001
PVD	440/2699	16%	<0.0001
CABG or Angioplasty (<1 Month)	877/6166	14%	<0.0001
Race: Black	352/3029	12%	0.0780
Age (By Year)			<0.0001



Summary and Conclusions

- Initiating treatment in hypertensive CAD patients with either a nondihydropyridine CA (verapamil SR)- or a beta-blocker (atenolol)-based BP treatment strategy results in **equivalent clinical outcomes and very similar blood pressure control**
- Either strategy requires **multiple drugs** (trandolapril and/or HCTZ) in most patients to achieve BP goals
- **Prevention of death and diabetes** by the CA strategy requires confirmation and could have important public health implications

