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Prospective, Randomized, Double-Blind, Placebo-controlled Trial of Erythropoietin in Patients With ST-Segment Elevation Myocardial Infarction Undergoing Percutaneous Coronary Intervention (REVIVAL-3)

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No conflict of interest to disclose



REVIVAL-3

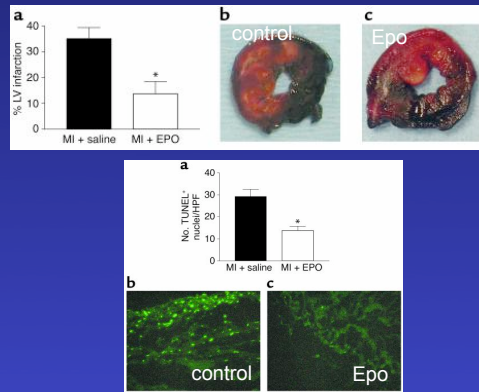
Background

Although primary percutaneous coronary interventions (PCI) improve survival of patients with acute myocardial infarction (AMI), ischemia/ reperfusion injury is still a major unresolved problem.

Experimental studies have shown a protective role of erythropoietin (Epo) during ischemia and reperfusion in the heart with a reduction in infarct size.

REVIVAL-3 Studies

Erythropoietin (Epo): Experimental



Epo reduces infarct size and improves myocardial function. This was associated with a decrease in apoptotic cells, an increase in EPC recruitment and neovascularization.

Parsa et al. 2003; Westenbrink et al. 2007



Reduction of infarct size in animal models of myocardial infarction was associated with an improve in mysocardial function, a decrease in apoptotic cell number within the infarct area, an increase in recruited endothelial progenitor cells with subsequent increased in neovascularization.

REVIVAL-3 Studies

Erythropoietin (EPO): Clinical

In patients with ischemic stroke high-dose Epoetin beta improved clinical outcome and reduced infarct size by trend (n=40)

Ehrenreich et al. 2002; Mol Med

In patients with AMI high-dose Darbopoietin was safe and well tolerated (n=22)

Lipsic et al. 2006 Cardiovascular Drugs and Therapy



So far only small clinical studies evaluated the effects of Epo as an adjunctive therapy to ischemic disease. High dose Epo within 8 hours applied to patients with ischemic stroke is safe and well tolerated and improved clinical outcome and reduced infarct size by trend. In patients with AMI high dose of the Epo analog Darbopoietin was safe and well tolerated. Yet a clinical benefit of this treatment has not been shown in AMI.

Objective...

... was to assess the effect of high-dose erythropoietin in patients with acute ST-elevation myocardial infarction treated with primary PCI

Patients with acute ST-elevation myocardial infarction with primary PCI

- chest pain lasting more than 20 min
- ≥ 0.1 mV of ST-segment elevation in ≥ 2 limb leads or ≥ 0.2 mV in ≥ 2 contiguous precordial leads or new left bundle branch block on surface ECG

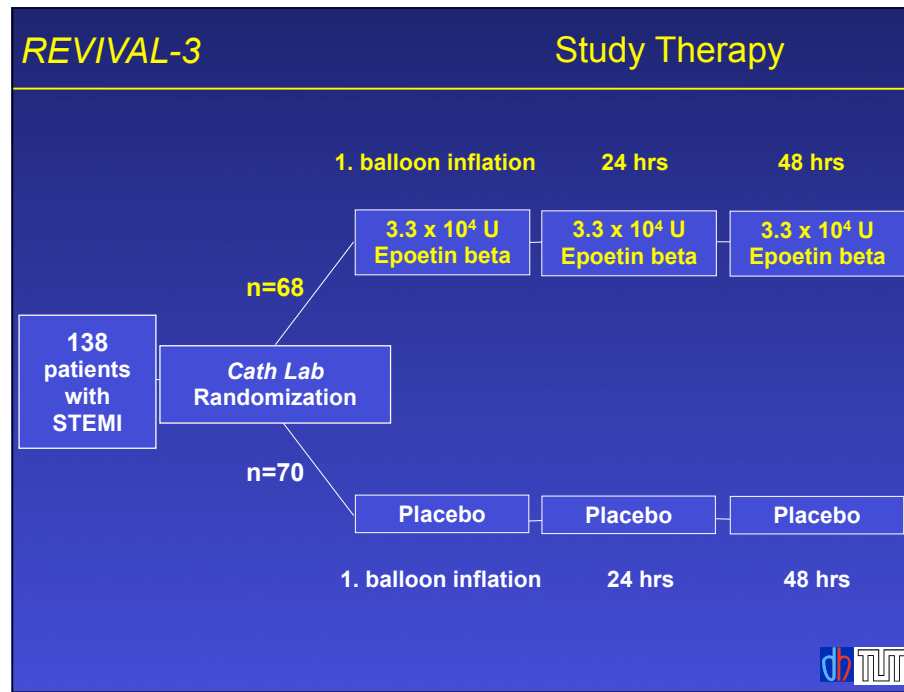
Angiographically left ventricular ejection fraction $< 50\%$

Written, informed consent



Patients with acute ST-elevation myocardial infarction with primary PCI were recruited for this study. They presented with characteristic prolonged chest pain and typical ECG changes. Angiographic EF had to be less than 50% and written informed consent was mandatory.

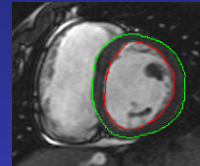
- Age > 80 or < 18 years
- Cardiogenic shock or prolonged cardiopulmonary resuscitation
- Previous MI
- Severe uncontrolled hypertension (>180mmHg, unresponsive to therapy)
- Hematological disorders such as essential thrombocytosis, megakaryoblastic leukemia, polycythemia vera
- Relevant hematologic deviations (hemoglobin < 10.0g/L or > 15.5 g/L, platelet count < $100 \times 10^9/L$ or > $600 \times 10^9/L$)
- Coronary intervention within the last 30 days
- Any contraindication to magnetic resonance imaging
- Known allergy to study medication, pregnancy, prior inclusion in the study



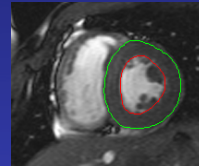
138 patients with STEMI were included in the study. Randomization was performed in the cath lab and after the 1.st balloon inflation 68 patients received epoetin beta and 70 patients received placebo in a double blinded manner. Study medication was repeated at 24 and 48 hours after primary PCI.

REVIVAL-3
Endpoint

Primary



EDV



ESV

$$EF = (EDV - ESV) / EDV * 100$$

Primary end point:

Left ventricular-EF at 6-month follow-up in MRI



Primary endpoint of the study was the left ventricular EF at 6 month follow-up measured by MR.

Key Secondary end points:

Change in LV-ejection fraction and infarct size over 6 months after randomization

Death, recurrent myocardial infarction, infarct related artery revascularization and stroke at 30 days and 6 months

Assumptions:

- LV-EF in placebo group: 45% ± 9%
- Increase in EF with Epo by 5%
- α -level: 0.05 (two-sided); power 80%

Sample size:


- **52** patients per group with MR study
- to accommodate for possible missing MR studies:
60 patients per group planned



Sample size calculation was based on the assumption that an average EF of 45% in the placebo group was increased by 5% with EPO and resulted in the number of 52 patients per group. To accommodate for possible missing MR studies the inclusion of 60 patients per group was planned.

| <i>REVIVAL-3</i> Characteristics | Patient | |
|-------------------------------------|---------------|-------------------|
| | Epo (n=68) | Placebo (n=70) |
| Age, yrs | 59±13 | 62±12 |
| Women, % | 18 | 26 |
| Hypercholesterolemia, % | 35 | 36 |
| Arterial hypertension, % | 63 | 63 |
| Diabetes mellitus, % | 16 | 14 |
| Current smoker, % | 43 | 43 |
| Body mass index, kg/m ² | 28±4 | 27±4 |


Mean±SD, %



Baseline characteristics, age, gender and risk factors were similar in both groups

| REVIVAL-3 | Infarct Characteristics | |
|--------------------------------|--------------------------------|---------------------------|
| | Epo (n=68) | Placebo (n=70) |
| Infarct localization, % | | |
| anterior | 49 | 43 |
| posterior | 43 | 50 |
| lateral | 8 | 7 |
| Killip Class, % | | |
| I | 75 | 72 |
| II | 22 | 27 |
| III | 3 | 1 |
| Symptom to admission [minutes] | 168 [109;315] | 175 [108;361] |
| Admission to PCI [minutes] | 84 [66;98] | 78 [57;96] |

%, Median [25th, 75th percentiles]

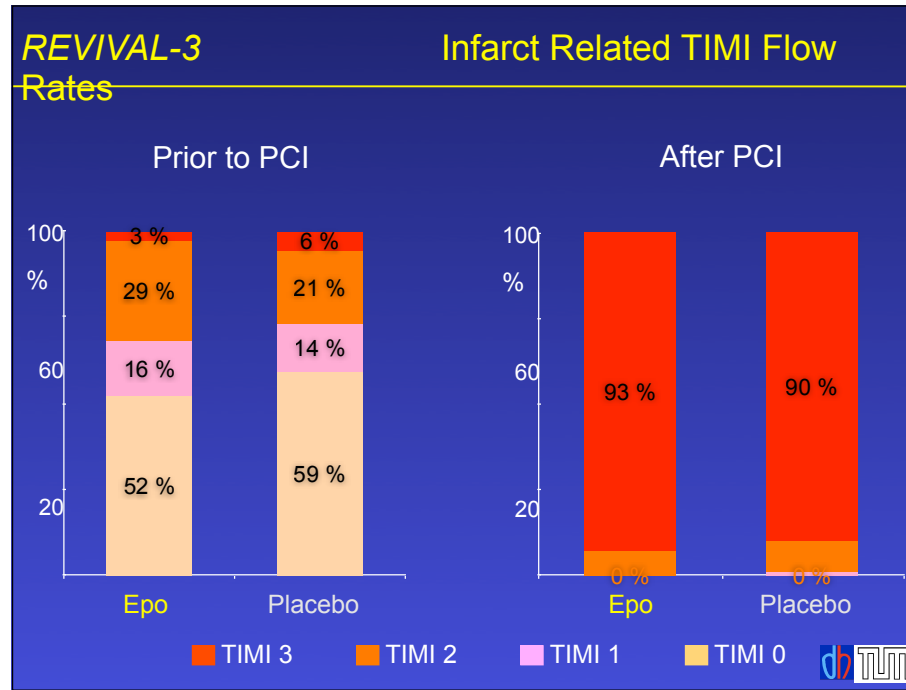


Both groups were also well matched regarding infarct localization, Killip class, duration of symptoms and door to balloon time.

| REVIVAL-3 | Infarct Characteristics | |
|------------------------------------|-------------------------|-------------------|
| | Epo (n=68) | Placebo (n=70) |
| LV- ejection fraction, % | 46±8 | 46±8 |
| Area at risk (SESTA-MIBI), % | 29±22 | 30±20 |
| Multivessel disease, % | 62 | 71 |
| Infarct related coronary artery, % | | |
| LAD | 50 | 44 |
| LCx | 6 | 9 |
| RCA | 44 | 46 |
| LMCA | 0 | 1 |
| Reperfusion strategy % | | |
| DES | 93 | 95 |
| BMS | 4 | 4 |
| PTCA | 3 | 1 |
| Mean±SD | | |

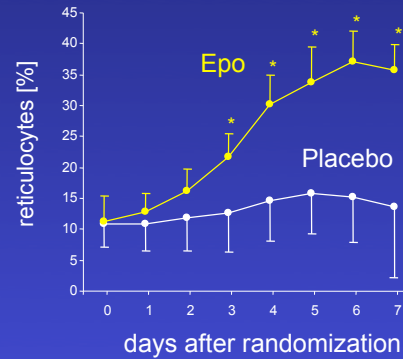


Baseline angiographic EF and area at risk measured by SESTA MIBI were similar in both groups. The extent of disease and infarct related coronary artery did not differ in both groups. Most of the patients received drug-eluting stents in the Epo as well as the placebo group.

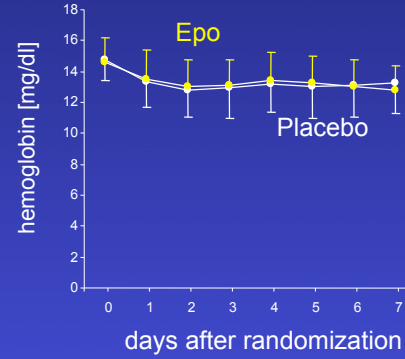


52% in the Epo group and 59% in the placebo group showed initial TIMI 0 flow. Successful PCI restored TIMI 3 flow in over 90% in both groups.

Reticulocytes



Hemoglobin

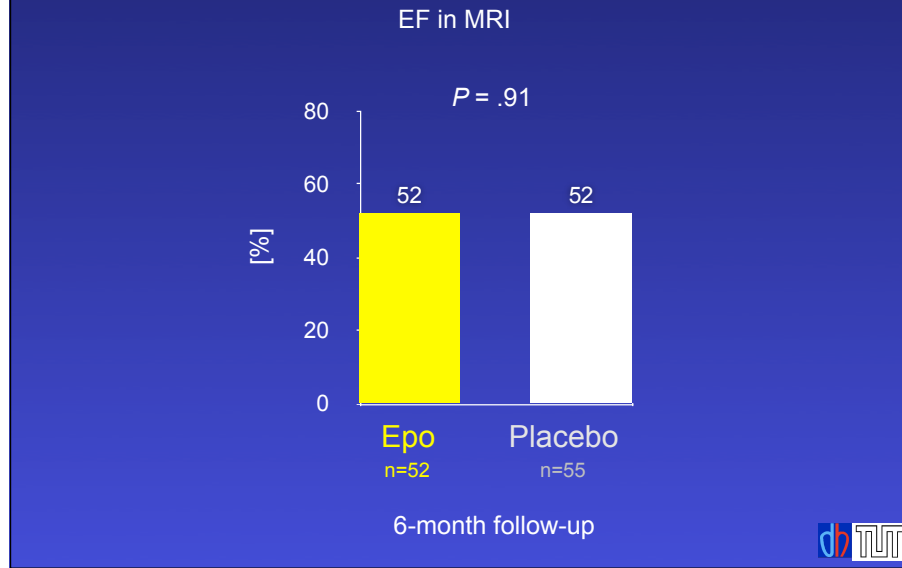


Mean±SD

* p < 0.05

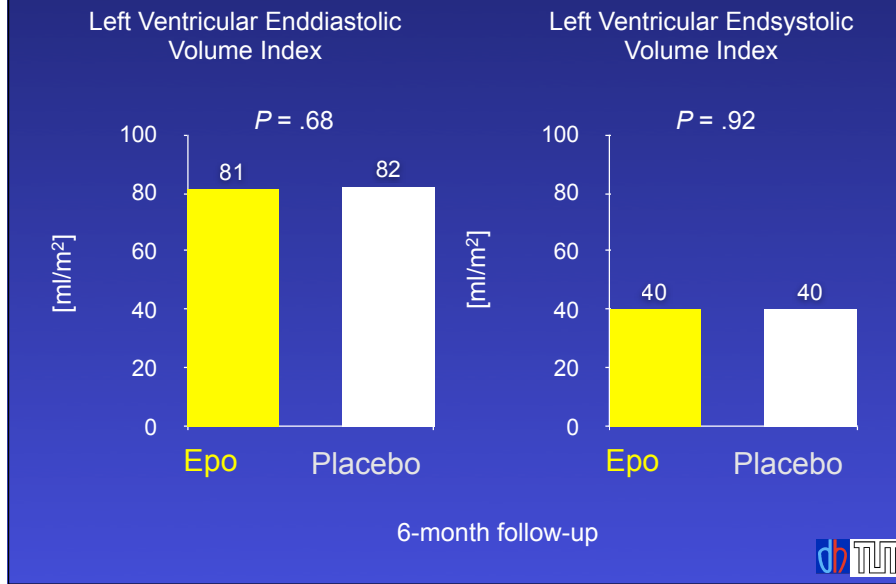


To measure the effect of Epo on erythropoiesis differential blood counts were analyzed. 3 days after the first application of epo we found a significant increase in the number of circulating reticulocytes that did not occur in the placebo group. Yet this increase in reticulocyte count was not sufficient to increase hemoglobin levels over the observation period.

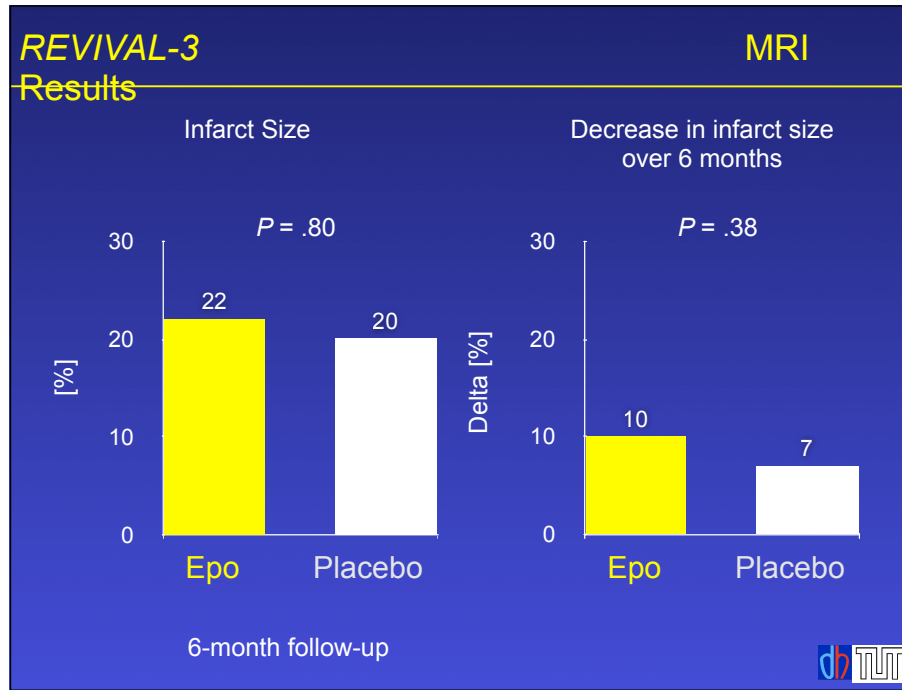


MRI studies were performed in 76% of the patients in the Epo group and 79% of the placebo group. At 6 month follow up EF in MRI was 52% in both groups. Thus treatment with epo did not improve left ventricular ejection fraction.

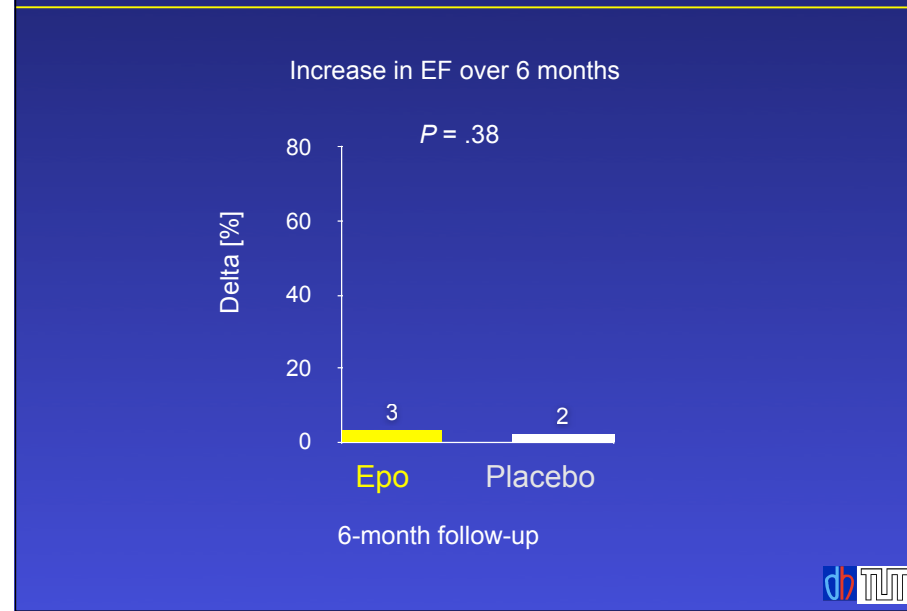
Results



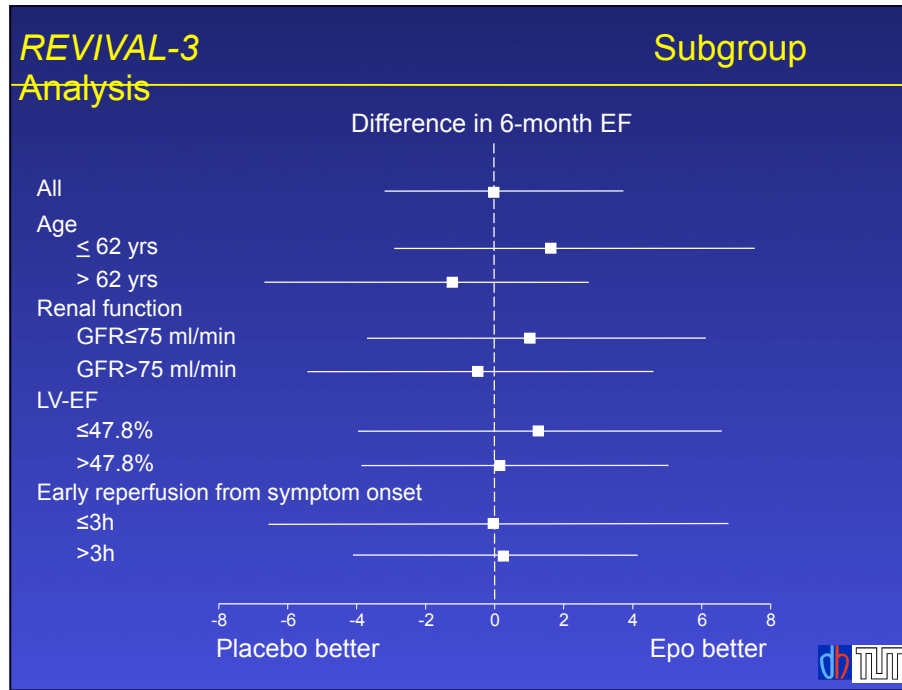
Similarly at 6 months follow up there were no difference in the enddiastolic volume index which and the endsystolic volume index. The enddiastolic volume index was 81 ml/m² in the Epo group and 82 in the placebo group. Endsystolic volume index was 40 ml/m² in both groups.



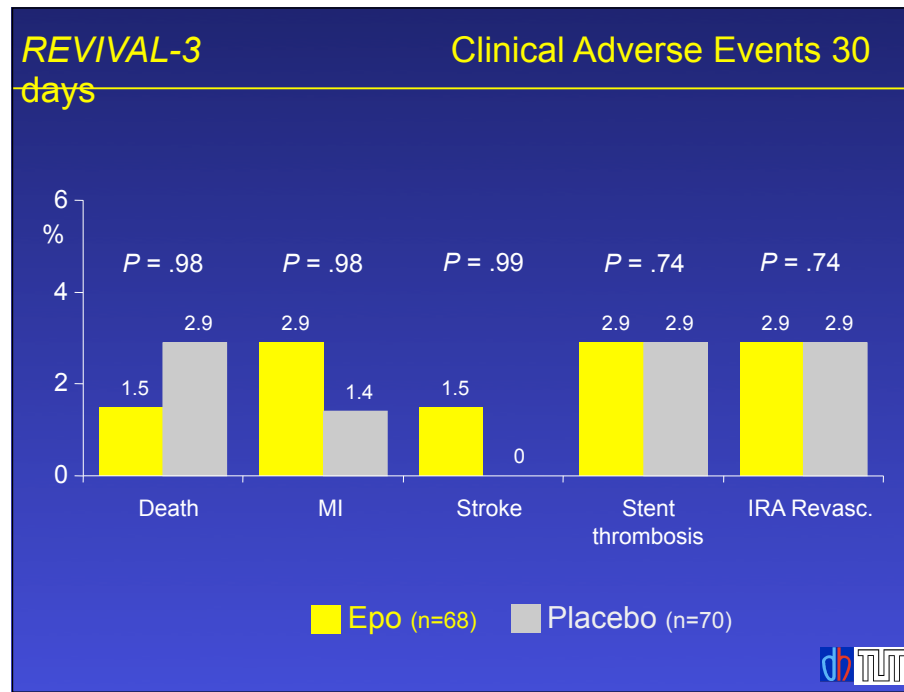
Infarct size in MRI at 6 months follow up was 22% after application of Epo and 20% after Placebo. Similarly when we analyzed the decrease in infarct size over 6 month we found a decrease in infarct size of 10% in the Epo group and of 7% in the placebo group. A difference that did not reach statistical significance.



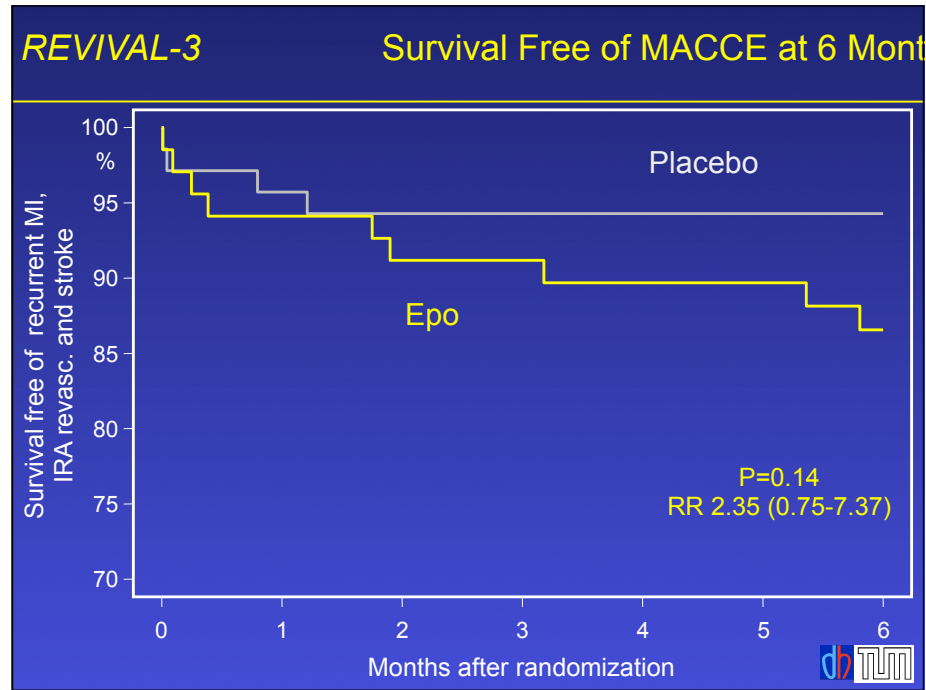
Follow-up angiography was performed in 84% of the Epo group and in 87% of the placebo group. Analysis of the baseline LV angiography and the angiography at 6 months follow up revealed an increase in EF of 3% in the Epo group and an increase of 2% in the Placebo group. Similarly the regional wall movement assessed by the number of hypokinetic cords showed no significant difference between the groups at 6 months follow-up.



Prespecified subgroups for assessment of potential treatment differences were defined. As shown in this slide there were no differences in 6 month EF in the younger or the older patients. Patients with impaired renal function or normal function did not benefit from EPO. Also patients with low or high LVEF at study entry or early or late reperfusion did not improve by the treatment with EPO.



Clinical follow up data at 30 days and 6 months were available in all patients. One patient died within 30 days after randomization in the Epo group and 2 in the placebo group. There were also no significant differences in the rate of MI, stroke, stent thrombosis and Infarct related artery revascularization.



In the patients receiving epo 13% experienced death, recurrent MI, infarct related artery revascularization or stroke as compared to 5.7% in the placebo group. Thus in the epo group the relative risk of MACCE was increased 2.35 a trend that did not reach statistical significance.

REVIVAL-3

Conclusion

High dose epoetin beta does not improve left ventricular function or reduce infarct size in patients with ST-elevation myocardial infarction treated with primary PCI.

The trend towards a higher risk of adverse clinical events should be taken into account before planning future investigations with this drug in patients with AMI.