# Stem cell therapy and proarrhythmia: a review of clinical experience

Joachim R. Ehrlich, MD, FESC

Department of Cardiology, Clinical Electrophysiology
Goethe-University, Frankfurt, Germany

# Presenter Disclosure Information

Financial Disclosures: none

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# Proarrhythmia with stem cell therapy

- significant proarrhythmic effects with intramyocardial injection of skeletal myoblasts (10 pts.)

Menasche et al. JACC 2003;41(7):1078-83

- intramyocardial injection of bone marrow-derived mononuclear cells (BMC) linked to arrhythmia (20 pts.)

Hendrikx et al., Circulation 2006;114(1 Suppl):I101-7

- No increase in occurrence of ventricular arrhythmias in larger controlled trials with i.c. BMC application

Wollert et al., Lancet 2004;364(9429):141-8
Assmus et al., NEJM 2006;355(12):1222-32

→→Ongoing debate regarding potential proarrhythmic effects of stem cell therapy

Ly&Nattel; Circulation. 2009;119:1824-1831
Macia&Boyden; Circulation 2009;119:1814-1823

# Skelettal myoblasts (CD56+)

Phase 1 clinical trial
10 pts. post-MI, LVEF <35%, scar, indication for CABG
Skelettal myoblasts – biopsies from the thigh
Injection across and around scar at time of surgery

| Patient No. | Age (yrs) | Myocardial Infarct | | NYHA Class | Cell Transplantation | | | Location of Bypass Grafts | LVEF (%) | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | Age | Location | | No. of Cells Injected ($\times 10^6$) | CD56+ (%) | No. of Injections | | PreTx | PostTx* |
| 1 | 72 | 2 years | Posterior | III–IV | 820 | 67 | 33 | LAD + Dg | 20 | 35 |
| 2 | 66 | 6 years | Anterior | III | 870 | 91 | 50 | OM ($\times 2$) | 25 | 27 |
| 3 | 67 | 9 and 3 years | Posterior | II | 620 | 97 | 57 | LAD + OM | 31 | 41 |
| 4 | 39 | 4 months | Posterolateral | II | 950 | 95 | 31 | LAD + IA | 22 | 45 |
| † 5 | 55 | 7 years and 5 and 3 months | Anterior | III–IV | 1,150 | 85 | 42 | RCA + IA | 34 | NA† |
| 6 | 52 | 5 years | Posterior | III | 880 | 96 | 36 | LAD + IA | 26 | 30 |
| 7 | 73 | 14 months | Anterior | III | 980 | 92 | 34 | RCA + IA | 28 | 32 |
| 8 | 69 | 3 months | Anterior | II | 1,100 | 85 | 35 | RCA + Dg | 25 | 29 |
| 9 | 51 | 19 years and 1 month | Anterior | II | 500 | 75 | 27 | OM + PLA + PDA | 18 | 25 |
| 10 | 67 | 13 years | Anterior | III | 840 | 81 | 31 | OM + IA | 24 | 25 |

sVT RBBB pattern in 4 patients (11-22d) post CABG

*Menasche et al. JACC 2003;41(7):1078-83*

# Bone-marrow derived cells (CD34+)

Randomized (1:1) clinical trial
20 pts. post-MI, scar, indication for CABG
Bone-marrow from sternal puncture (7ml)
Injection at border zone at time of surgery

| | CTL LVEF | BMC LVEF | P-value |
|---|---|---|---|
| Baseline | 39.5±5.5 | 42.9±10.3 | 0.19 |
| Postop. | 41.2±10.1 | 45.8±13.2 | 0.33 |
| 4 month | 43.1±10.9 | 48.9±9.5 | 0.25 |
| Change | 3.6±9.1 | 6.1±8.6 | 0.41 |

VT inducible in 0 / 5 CTL pts. but 6 / 9 BMC pts.

*Hendrikx et al., Circulation 2006;114(1 Suppl):I101-7*

# BOOST (CD34+ cells)

Randomized (1:1) clinical trial
60 pts. after PCI for acute MI
Bone-marrow from iliac crest (~128 ml)
i.c. application of BMC cells 4.8±1.3 days after MI
Stop-flow technique, infarct-related artery

| | CTL LVEF | BMC LVEF | P-value |
|---|---|---|---|
| Baseline | 51.3±9.3 | 50.0±10.00 | |
| 6 months | 52.0±12.4 | 56.7±12.5 | |
| Change | 0.7±8.1 | 6.7±6.5 | 0.0026 |

No difference in ventricular premature beats on holter
VT/VF inducible in 1 / 28 CTL pts. and 2 / 27 BMC pts.

*Wollert et al., Lancet 2004;364(9429):141-8*

# REPAIR-AMI (CD34+ cells)

Randomized (1:1) clinical trial
204 pts. after PCI for acute MI
Bone-marrow from iliac crest (~50 ml)
i.c. application of BMC cells 2-7 days after MI
Stop-flow technique, infarct-related artery

| | CTL LVEF | BMC LVEF | P-value |
|---|---|---|---|
| Baseline | 46.9±10.4 | 48.3±9.2 | n.s. |
| 4 months | 49.9±13.0 | 53.8±10.2 | 0.02 |

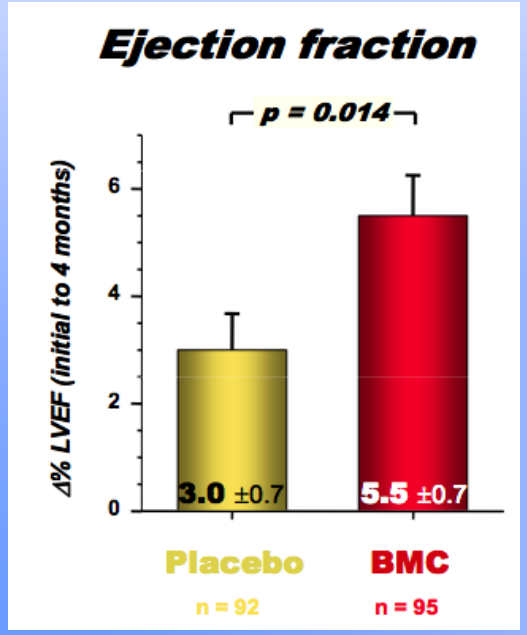
Documented ventricular arrhythmia or syncope
4 months - 4 / group
1 year - 5 / group

*Schächinger et al. N Engl J Med. 2006 Sep 21;355(12):1210-21*

# i.c. progenitor cell therapy

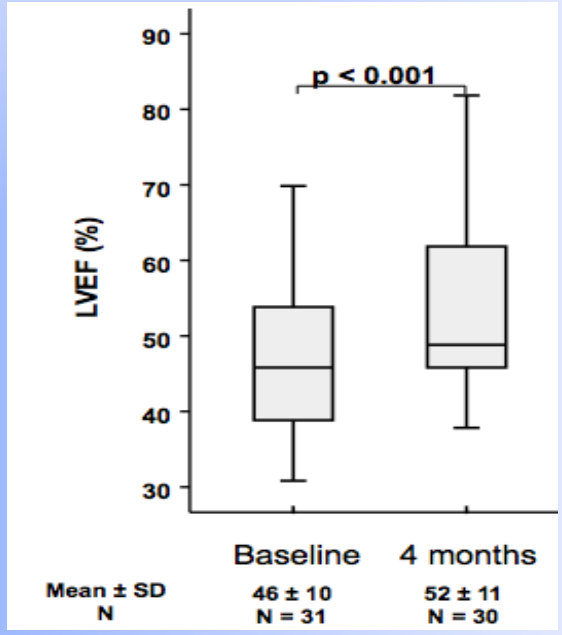
intracoronary administration of bone marrow-derived progenitor cells effective therapy for patients with:

## Acute myocardial infarction (AMI)



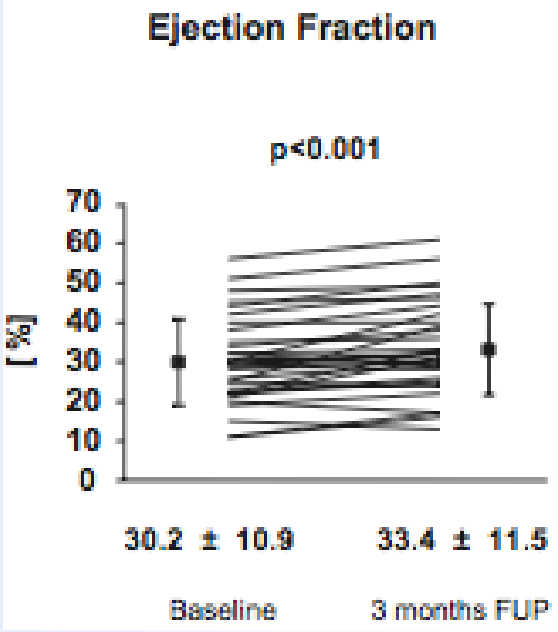

Schächinger et al., N Engl J Med 2006

## Chronic ischemic heart failure (ICM)




Assmus et al., N Engl J Med 2006

## Dilated Cardiomyopathy




Fischer-Rasokat et al., Circ Heart Fail 2009

# Case-control study

112 patients with chronic heart failure (ICM/DCM)
with prior ICD and
treatment with intracoronary BMC therapy
**study group**

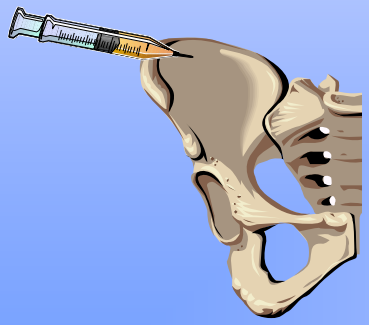
**matched 1:2** according to age, gender and LV-EF

224 patients with chronic heart failure (ICM/DCM)
with implantation of an ICD system
**control group**

*Leistner et al. Eur Heart J. 2011 Feb;32(4):485-91*

# Method of BMC therapy

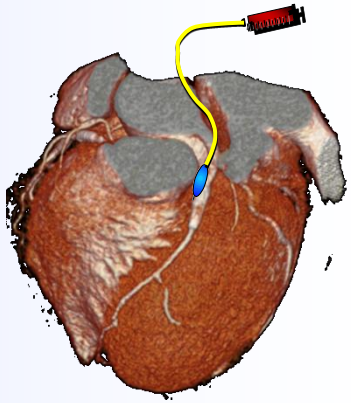
- therapy was performed at our institution
  either in the TOP-CARE DCM trial or
  an observational registry study (clinicaltrials.gov-ID´s: NCT00284714 and NCT00962364)
- Cell-separation was performed by the Ficoll method
- autologous bone marrow derived mononuclear cells (BMC)
- BMC´s were transplanted intracoronary



**Bone marrow aspiration**

**Cell Processing by the Ficoll method**

**BMC**



*Leistner et al. Eur Heart J. 2011 Feb;32(4):485-91*

# Study design and methods

**112** patients with chronic heart failure and implanted ICD and intracoronary administration of autologous BMC therapy between 2002-2008

**224** patients with chronic heart failure **without** BMC therapy and ICD implant between 1997-2007

Retrospectively matched 1:2 for age, LV-EF and gender (retrospective case-control study)

follow up 4-6, 12 and 24 month

- ICD documented VT/VF episodes
- ICD or ECG documented AF episodes
- Sudden Cardiac Death (SCD)

# Baseline characteristics

| | BMC treated patients (n=112) | Control group (n=224) | p -value |
|---|---|---|---|
| Age (yrs.) | 61.8 ± 11.2 | 61.5 ± 11.5 | 0.89 |
| Gender (male) (%) | 83.0 | 83.9 | 0.75 |
| LV-EF (%) | 23.8 ± 7.8 | 24.4 ± 8.3 | 0.46 |
| Diabetes (%) | 28.6 | 29.9 | 0.89 |
| CAD (%) | 73.2 | 63.3 | 0.07 |
| Atrial fibrillation (%) | 36.8 | 26.1 | 0.06 |
| NYHA class | 2.3 ± 0.7 | 2.3 ± 0.8 | 0.74 |
| Nt-pro-BNP (pg/ml) | 2966 ± 2566 | 2449 ± 2262 | 0.65 |
| Serum creatinine (mg/dl) | 1.33 ± 0.6 | 1.24 ± 0.7 | 0.20 |

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# Baseline characteristics

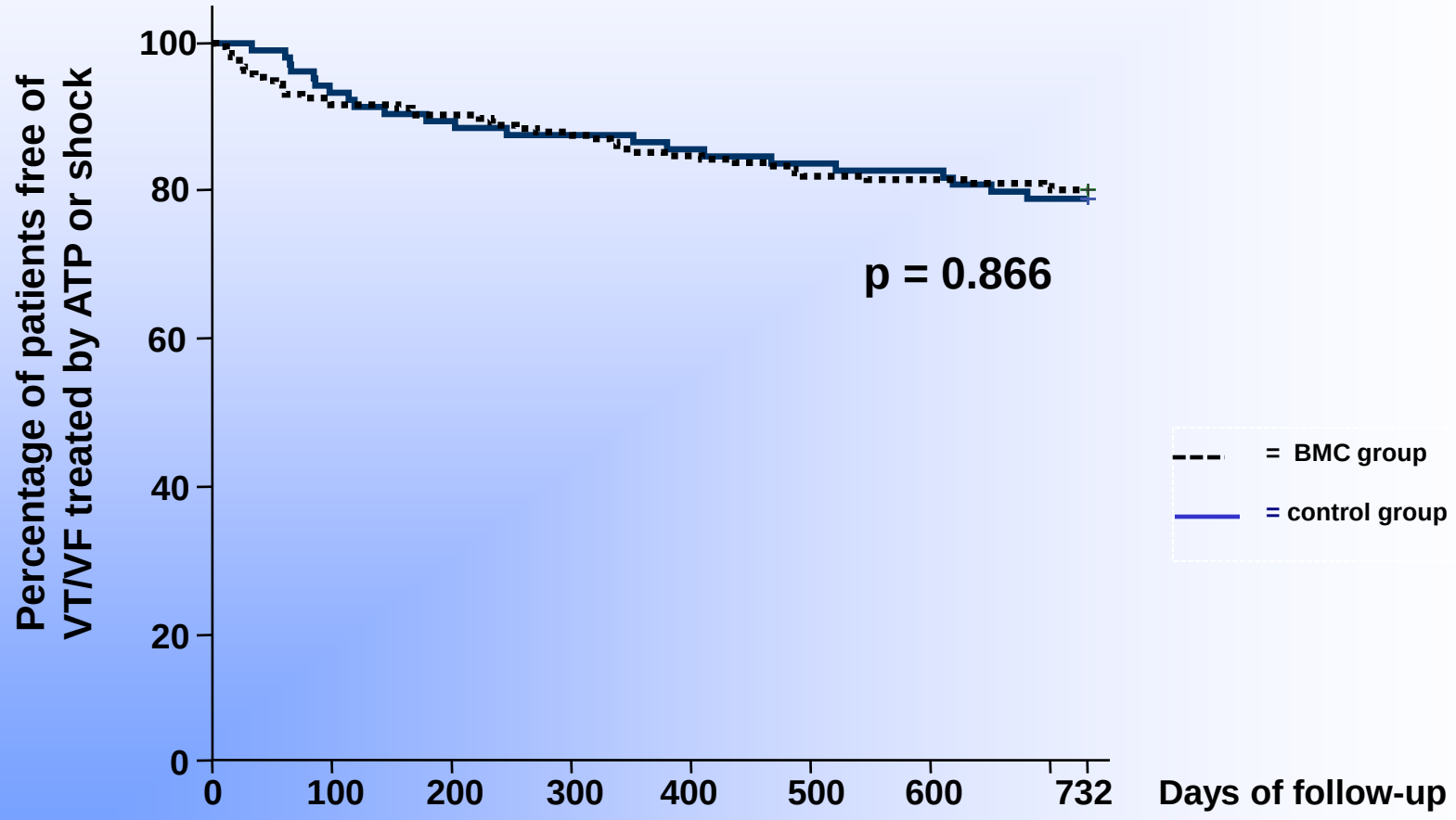
| | BMC treated patients (n=112) | Control group (n=224) | p - value |
|---|---|---|---|
| **Implanted ICD-type** | | | |
| - 1-chamber (%) | 60.4 | 47.4 | |
| - 2-chamber (%) | 19.8 | 24.1 | 0.11 |
| - 3-chamber (%) | 19.8 | 28.1 | |
| **Indication for ICD therapy** | | | |
| - primary prevention of SCD (%) | 61.6 | 64.7 | |
| - secondary prevention of SCD (%) | 36.6 | 35.3 | 0.72 |
| - unknown | 1.8 | ---- | |
| **Antiarrhythmic therapy** | | | |
| - beta-blocker (%) | 91.7 | 83.4 | 0.93 |
| - amiodarone (%) | 22.3 | 16.8 | 0.23 |
| - other antiarrhythmic drugs (sotalol, mexiletine (%)) | 2.7 | 4.4 | 0.55 |

# Incidence of VT/VF episodes

**Incidence of episodes of ventricular tachycardia (VT) and ventricular fibrillation (VF) during the 2-year follow-up**

| | BMC treated patients (n=112) | Control group (n=224) | p - value |
|---|---|---|---|
| **Ventricular tachycardia** | | | |
| - total (%) | 25.0 | 27.1 | 0.78 |
| - treated by ATP (%) | 18.8 | 19.6 | 0.88 |
| - treated by shock (%) | 10.4 | 9.0 | 0.83 |
| **Ventricular fibrillation** (%) | 5.2 | 6.5 | 0.80 |

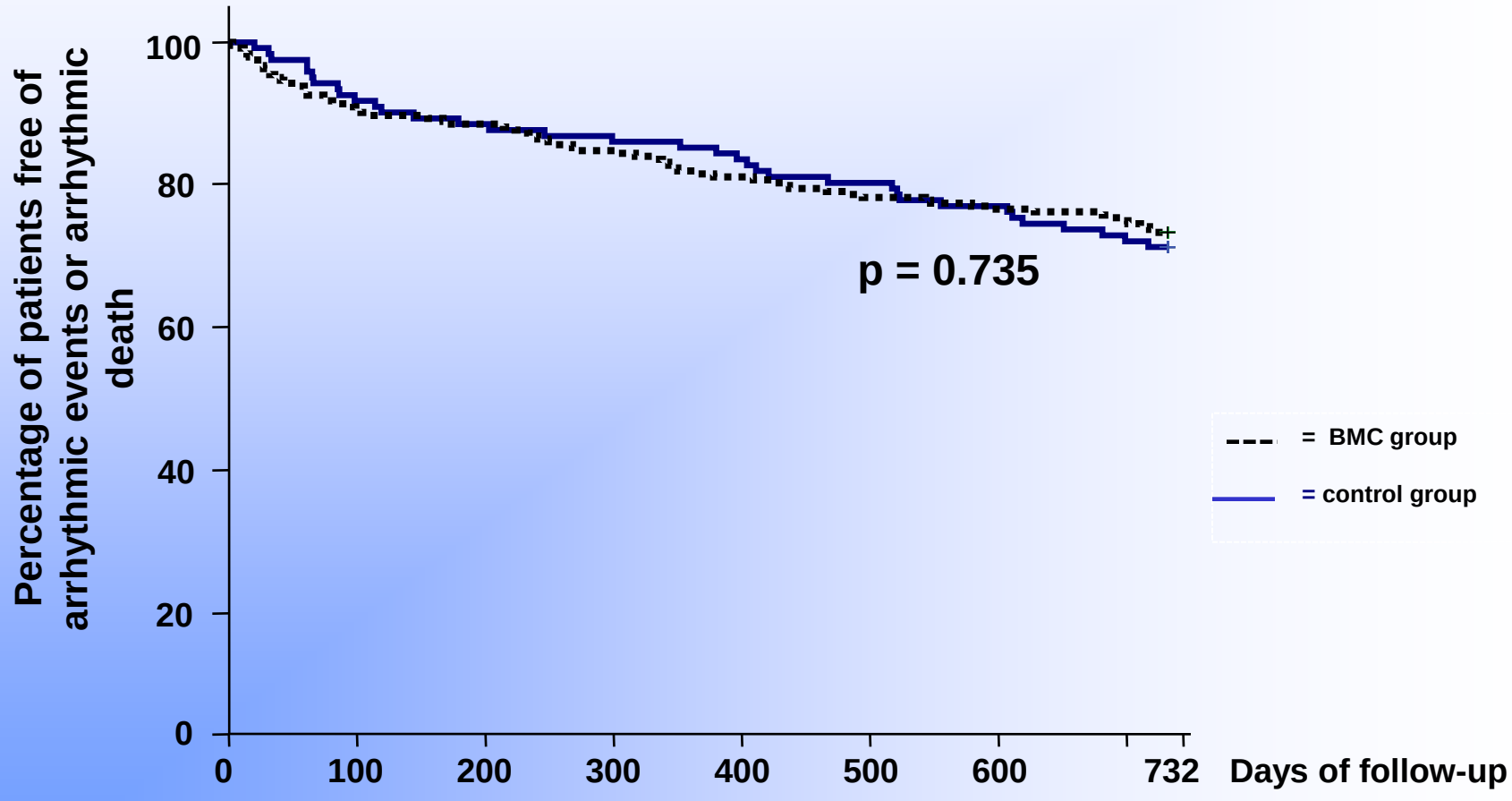
# Freedom from treated VT/VF




| No. at risk: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| BMC group: | 112 | 103 | 99 | 96 | 92 | 86 | 81 | 73 |
| Control group: | 224 | 204 | 200 | 193 | 189 | 166 | 157 | 151 |

*Leistner et al. Eur Heart J. 2011 Feb;32(4):485-91*

# Freedom from treated VT/VF or SCD




| No. at risk: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| BMC group: | 112 | 101 | 97 | 94 | 90 | 84 | 73 | 67 |
| Control group: | 224 | 202 | 197 | 190 | 186 | 165 | 149 | 139 |

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# Predictors of treated VT/VF episodes or SCD

| | Hazard Ratio | 95% Confidence Interval | p - value |
|---|---|---|---|
| **Baseline Chraracteristics:** | | | |
| - Age | 1.00 | 0.98 – 1.02 | 0.75 |
| - Male gender | 1.93 | 0.93 – 3.99 | 0.05 |
| - NYHA class | 1.54 | 1.02 – 1.98 | 0.03 |
| - LV-EF ≤ 30% | 1.32 | 0.74 – 1.88 | 0.10 |
| - QRS ≥ 120ms | 1.61 | 1.03 – 2.50 | 0.03 |
| - Systolic blood pressure ≤ 100mmHg | 1.29 | 1.08 – 1.49 | 0.04 |
| - CAD | 1.02 | 0.88 – 1.17 | 0.77 |
| - Duration of CHF | 1.00 | 1.0 – 1.0 | 0.13 |
| **Arrhythmic History:** | | | |
| - AF at baseline | 1.10 | 0.63 – 1.93 | 0.74 |
| - Secondary prevention of SCD | 2.10 | 1.35 – 3.22 | 0.001 |
| **CHF – Treatment:** | | | |
| - Intracoronary BMC administration | 1.00 | 0.64 – 1.58 | 0.99 |
| - Beta-blocker therapy | 0.58 | 0.31 – 1.06 | 0.08 |
| - Amiodarone therapy | 0.74 | 0.40 – 1.36 | 0.74 |

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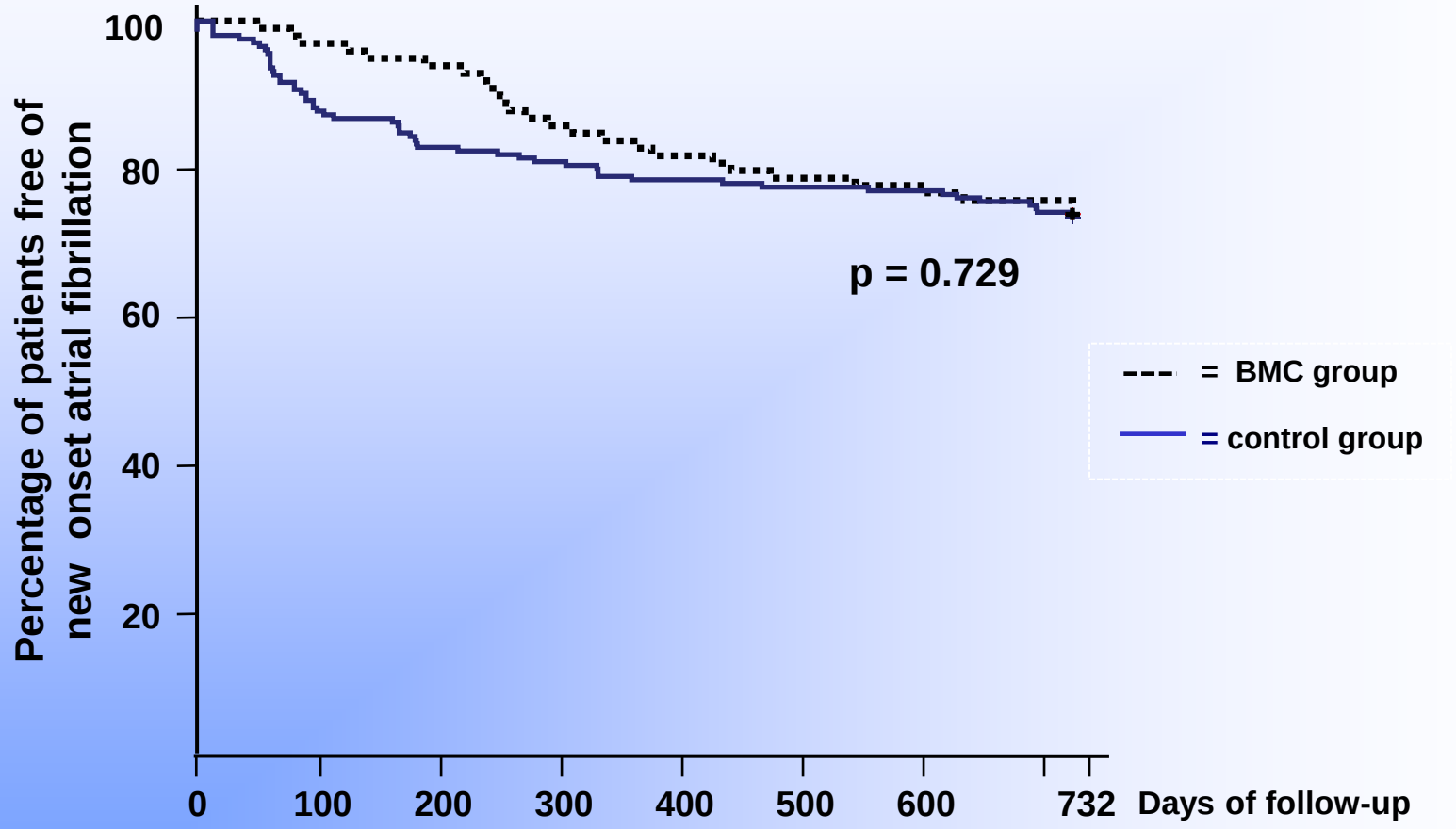
# New onset of atrial fibrillation




| No. at risk: | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| BMC group: | 71 | 67 | 63 | 55 | 48 | 45 | 43 | 34 |
| Control group: | 165 | 138 | 126 | 120 | 109 | 107 | 104 | 90 |

*Leistner et al. Eur Heart J. 2011 Feb;32(4):485-91*

# Summary

There was:

1. No influence on sudden cardiac death

2. No influence on incidence of or time to VT/VF episodes

3. No influence on new onset of atrial fibrillation

of i.c. BMC-therapy in heart failure patients

# Conclusion

Proarrhythmic risk potentially depending on application (intra-myocardial injection) or cell type (SkM)

No evidence for proarrhythmic risk in patients treated with intra-coronary BMC application

Further prospective randomized data should be collected

# Thank you