

# Role of Statins in Heart Failure

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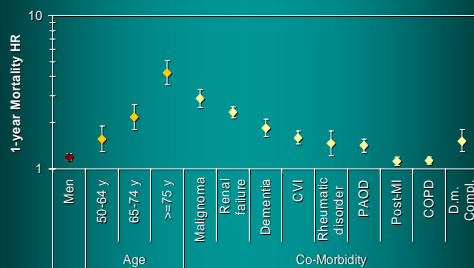


## Role of Statins in Heart Failure

- /// Background - Why could it be controversial?
- /// Prevention of heart failure by statins
- /// Evidence from other heart failure trials and registries
- /// CORONA
- /// What to do based on these results?



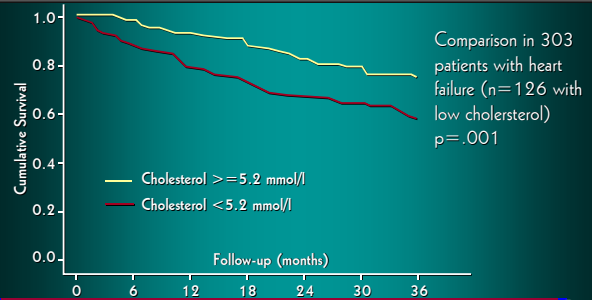
## One-Year Mortality After First CHF Hosp. In 38'702 Pat.



Jong et al. Arch Intern Med 2002; 162: 1689



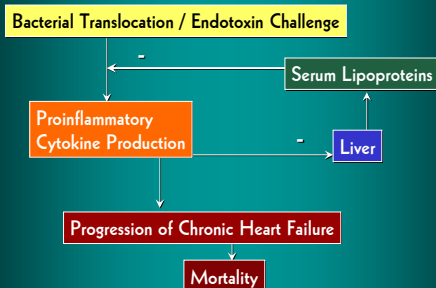
## Low Cholesterol as a Poor Predictor of Outcome in Heart Failure



Rauchhaus et al. JACC 2003; 42: 1933



## The Endotoxin-Lipoprotein Hypothesis



Rauchhaus et al. Lancet 2000; 356: 930

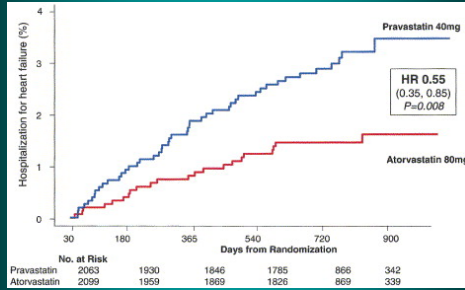


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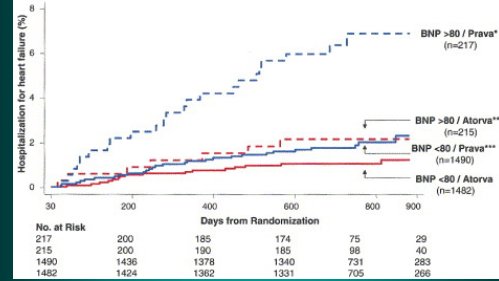


## Effects of Intensive Lipid Lowering on Heart Failure Events (PROVE-IT)



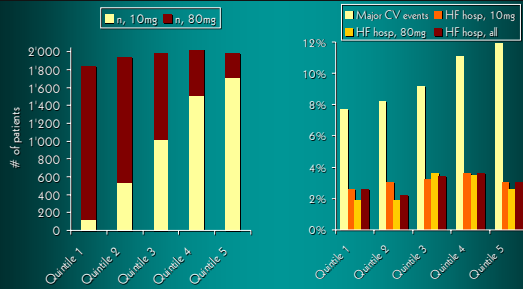
Scirica et al. JACC 2006, 47: 2326

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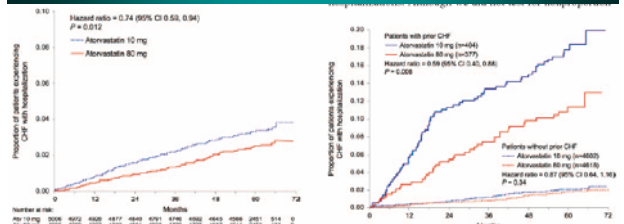
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## CHF Hospitalisations in Relation to Serum Cholesterol and Atorvastatin Dose



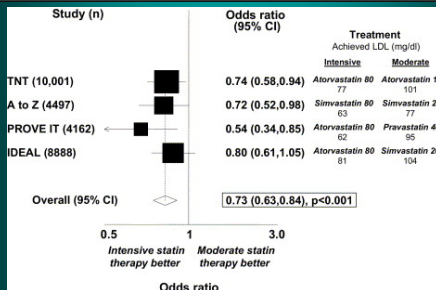
Khush et al. Circulation 2007, 115: 576

## Reduction of Events by Statin Therapy in CHF - Subgroups from TNT Trial



Khush et al. Circulation 2007, 115: 576

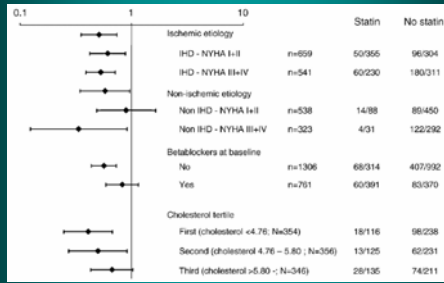
## Risk Reduction of Heart Failure Events due to Statin Therapy?



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## Statins in Heart Failure - Registry-Data from 5 Centres in Europe



Anker et al. Int J Cardiol 2006, 112: 234

## Are Statins Beneficial in Heart Failure ? Retrospective Analyses

	ELITE-2: n=2734 / 398		Registry: n=1363 / 705	
	HR	p	HR	p
LVEF (%)	0.97	<0.0001	0.96	<0.0001
Ischemic	1.58	<0.0001	1.18	0.23
Age (y)	1.03	<0.0001	1.04	<0.0001
BMI (kg/m <sup>2</sup> )	0.96	0.0002	0.97	0.03
Chol. (mmol/l)	0.88	0.0008	0.89	0.02
Statin use	0.61	0.003	0.64	0.005
β-Blocker	0.63	0.0003	0.66	0.006
NYHA	1.89	<0.0001	1.79	<0.0001

CAVE: Large differences between groups  
Anker et al. Int J Cardiol. 2006, 112: 234

## Are Statins Beneficial in Heart Failure ? Retrospective Analysis CIBIS-II

	Statin		No statin		p interaction univar.	p interaction multivar.
	Bisopro	Placebo	Bisopro	Placebo		
Death	1.7%	17.9%	12.8%	17.2%	0.003	<.0001
SCD	0.0%	10.4%	4.0%	5.9%	0.03	0.03
CHF death	0.0%	1.9%	3.0%	3.7%	0.02	0.5
CV death	1.7%	14.2%	9.7%	12.0%	0.003	0.004
Hosp CHF	7.5%	13.2%	12.4%	18.0%	0.001	0.0002
CV death / hosp	25.0%	43.4%	29.7%	34.4%	0.08	0.001

CAVE: Large differences between groups  
Krum et al. Cardiology 2007, 108: 28

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## CORONA Inclusion Criteria

- Patients with ischemic heart failure, aged 60 years or older
- NYHA II, III, IV
- LVEF ≤40% (LVEF ≤35% in NYHA II)
- „investigator thought they did not need statin treatment...“
- No acute decompensation
- No ICD / CRT within 3 months
- No infarction with 6 months, no PCI, CABG, unstable angina, stroke within 3 months
- Liver enzymes max 2x ULN (CK 2.5x ULN); creatinine ≤2.1

Kjekshus et al. NEJM 2007, 347: 2248

## CORONA Baseline characteristics

	Rosuva (10mg)	Placebo	P
Age	73 ± 7 years	73 ± 7 years	.99
Female sex	24%	24%	.98
NYHA II / III / IV	37 / 62 / 1.6%	37 / 61 / 1.4%	.61
LVEF	31 ± 7	31 ± 7	.94
BMI	27 ± 5	27 ± 5	.54
Previous MI	60%	60%	.87
Cholesterol	5.35 ± 1.06	5.36 ± 1.11	.77
NT-BNP (pmol/l)	166 median	180 median	.13
Syst BP	129 ± 17	129 ± 17	.52

Kjekshus et al. NEJM 2007, 347: 2248

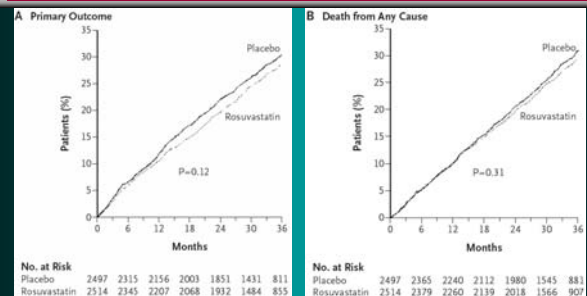
## CORONA Baseline characteristics

- /// Patients were well treated overall
  - /// ACE-inhibitor or ARB: 92%
  - ///  $\beta$ -Blocker: 75%
  - /// Spironolactone: 39%
  - /// Loop diuretic: 76%
  - /// Digoxin: 33%
- /// 24% patients had serum creatinine  $>130\mu\text{mol/l}$
- /// Mean creatinine:  $115 \pm \mu\text{mol/l}$
- /// LDL-levels:  $3.55 \pm 0.94 \text{ mmol/l}$

Kjekshus et al. NEJM 2007, 347: 2248



## Outcome in CORONA 1° EP: CV death, MI, stroke



Kjekshus et al. NEJM 2007, 347: 2248



## Outcome in CORONA

- /// Similar results on basically all prespecified fatal and non-fatal events (HR between 0.92 and 1.00, no significance)
- /// However, reduction in some hospitalisation rates:
  - /// Any cause: 0.94 ( $p=0.09$ )
  - /// CV cause: 0.92 ( $p=0.04$ )
  - /// Worsening heart failure: 0.91 ( $p=0.11$ )
  - /// Unstable angina: 0.91 ( $p=0.56$ )
  - /// Non-CV cause: 0.98 ( $p=0.72$ )
- /// Side effects similar in both groups

Kjekshus et al. NEJM 2007, 347: 2248



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## Why is There No Risk Reduction in CORONA? - Possible Explanations

- /// Rosuvastatin might have a profile different to that of other statins (apart from the effects on lipids and CRP)
  - /// Class effect apart from effects on muscles (and liver)
- /// Study too small for positive effects
  - /// Discrepancy between positive effects on hospitalisations and lacking effects on mortality and primary endpoint
- /// Overall relative few vascular events
  - /// But CHF and SCD in previous trials often related to myocardial infarction
- /// Other problems main problem / interactions !



## Why is There No Risk Reduction in CORONA? - Possible Explanations

- /// Otherwise very well treated patients
  - /// Additional effect only small?
- /// Subgroup analyses
  - /// „The effect of treatment was consistent across all subgroups of patients with prespecified risks, with no indication of harm in any subgroup“
- /// Combination of older age and heart failure may result in lesser importance of cardiovascular targets (particularly prevention)
- /// Too late for prevention !

BMI	Placebo	Rosuvastatin
$\geq 26$	413/1538 (11.0)	365/1563 (9.3)
$< 26$	319/954 (14.7)	324/942 (15.1)



## Consequences of CORONA

Should we treat heart failure patients with statins ?

- /// Patients without coronary artery disease not
- /// Based on the overwhelming evidence for secondary prevention of CAD principally yes, but ...
- /// Consideration of potential benefit in view of the individual prognosis
  - /// Positive effects of statins need some time... (1-2 years)
- /// In patients with advanced / end-stage heart failure, statins may not be first line treatment



## Statins and Heart Failure

- /// Evidence so far rather poor
  - /// Indirect evidence mainly suggests improvement in prognosis
  - /// But there are some arguments for the opposite
  - /// CORONA study overall disappointing
- /// Assessment of the individual prognosis
  - /// Prognosis of the underlying disease(s)
  - /// Possible effects of secondarily preventive means
- /// Heart failure *per se* no reason for using statins

