Heart Rate Modulation

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Factors and conditions influencing HR

Factors and conditions	Heart rate increase +/decrease −
Non-modifiable	
Increasing age	−
Female sex	+
Genetic	+/−
Physiological	
Early morning hours	+
Night time	−
Supine to standing	+
Mental–physical stress	+
Lifestyle	
Physical training	−
Obesity	+
Smoking	+
Alcohol abuse	+
Pathological	
Hyperlipidaemia	+
Obesity	+
Poor cardiorespiratory fitness	+
Heart failure	+
Medications (β-blockers/-stimulants)	−/+

Resting HR vs. Mortality

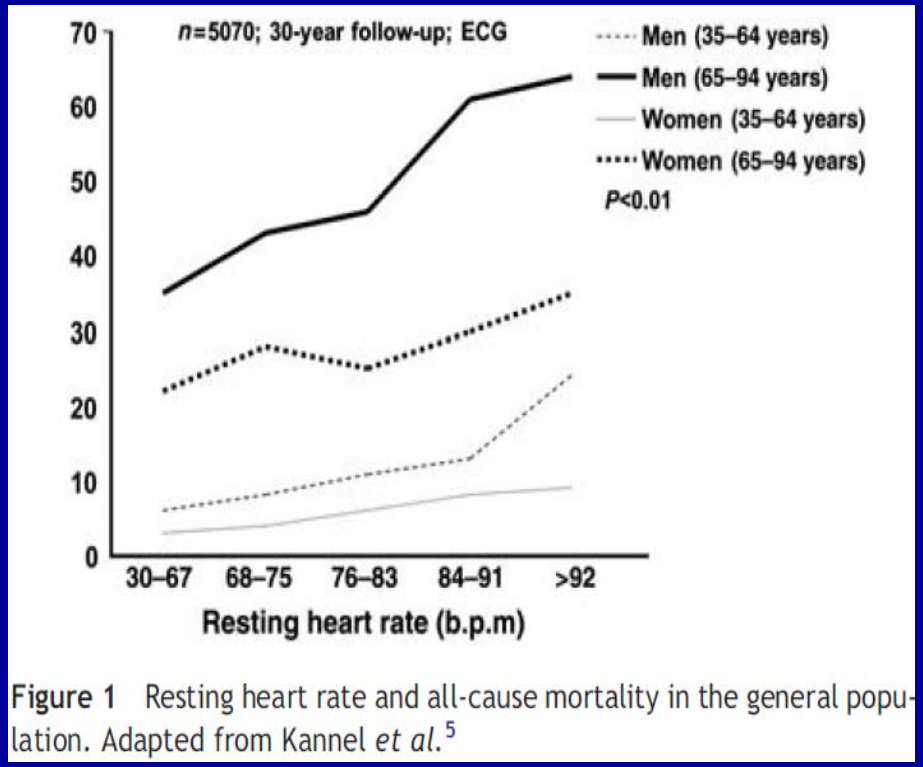
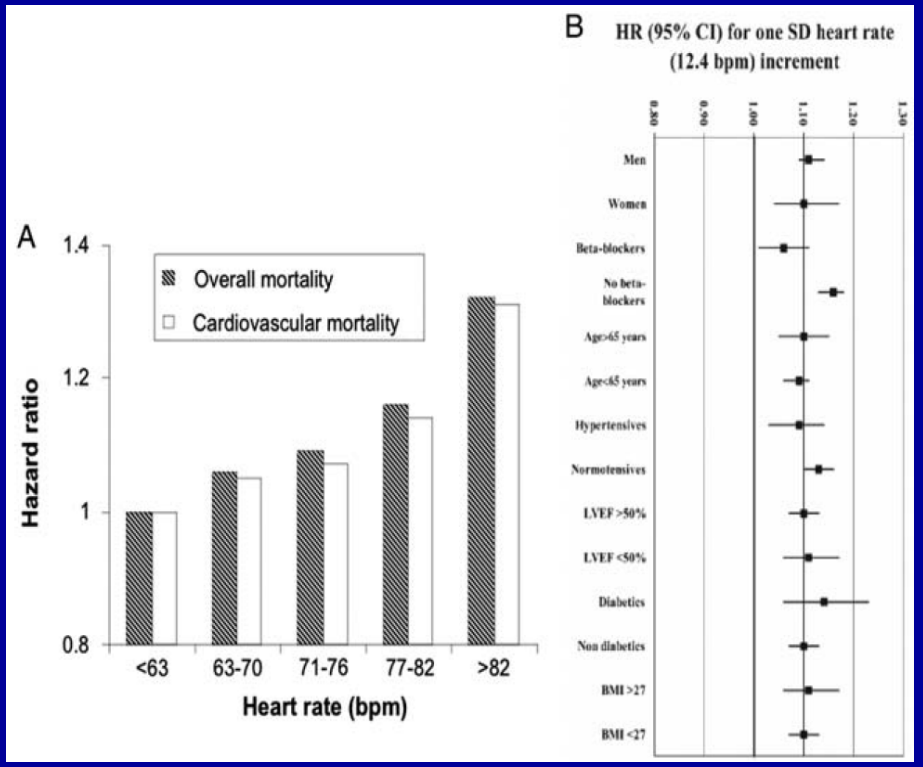
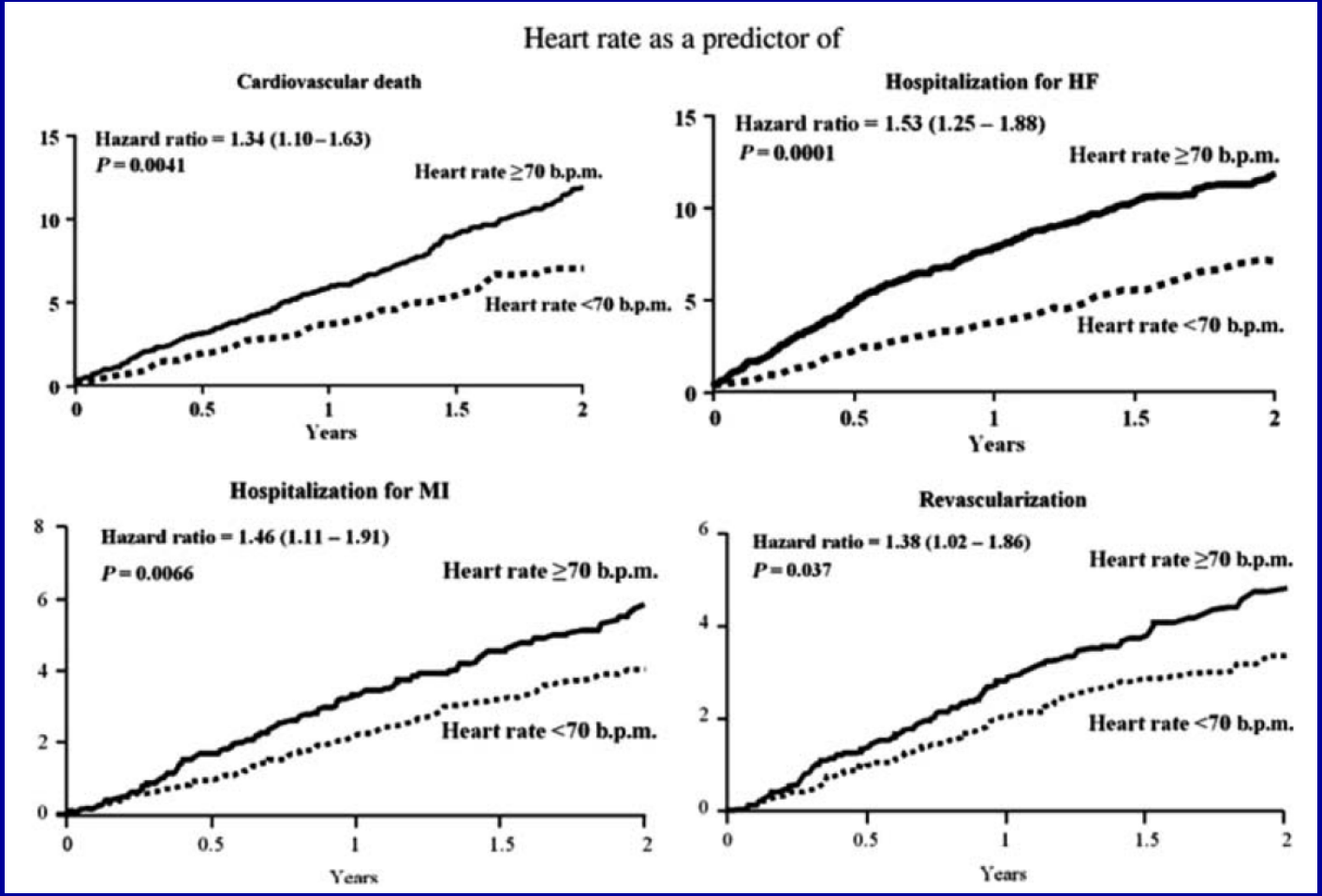


Figure 1 Resting heart rate and all-cause mortality in the general population. Adapted from Kannel *et al.*[5]

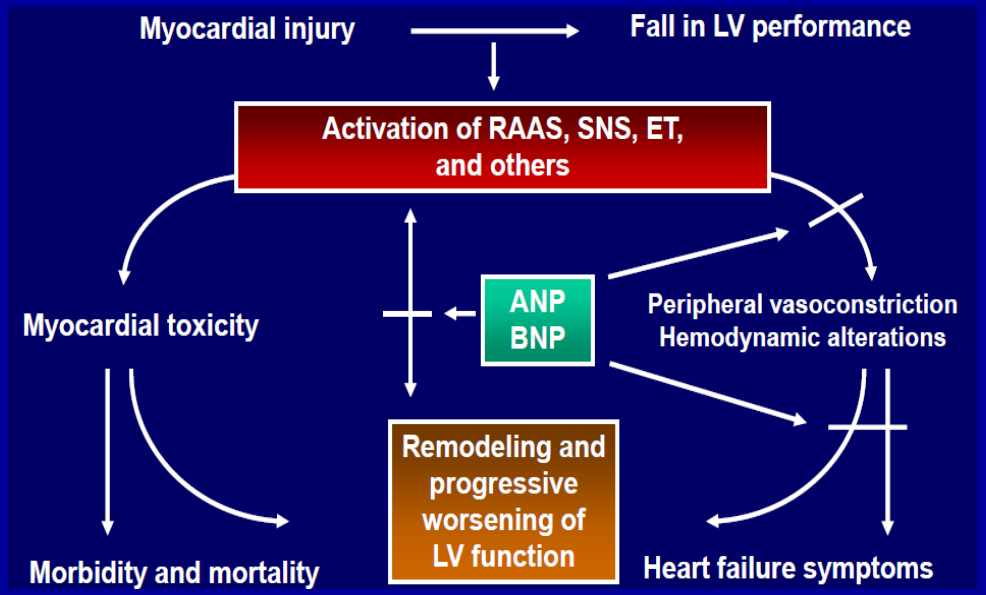


Heart Rate as a predictor of



Heart Rate in Heart Failure

- Risk Factor? or Risk Marker?
- Enhanced HR
  - marker of excessive neuroendocrine activation
  - Beneficial compensatory response, up to certain point
  - Preserves CO. but, impaired LV filling, ↑MO_2 consumption ↓coronary perfusion

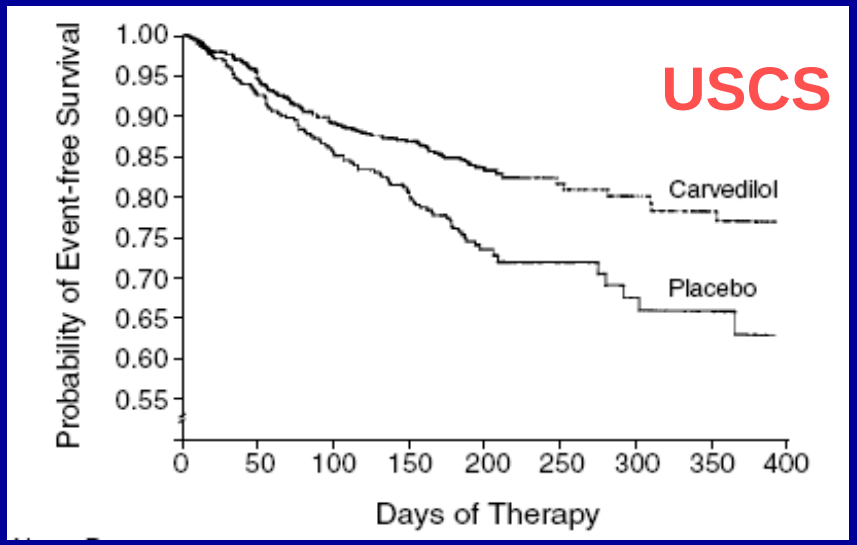


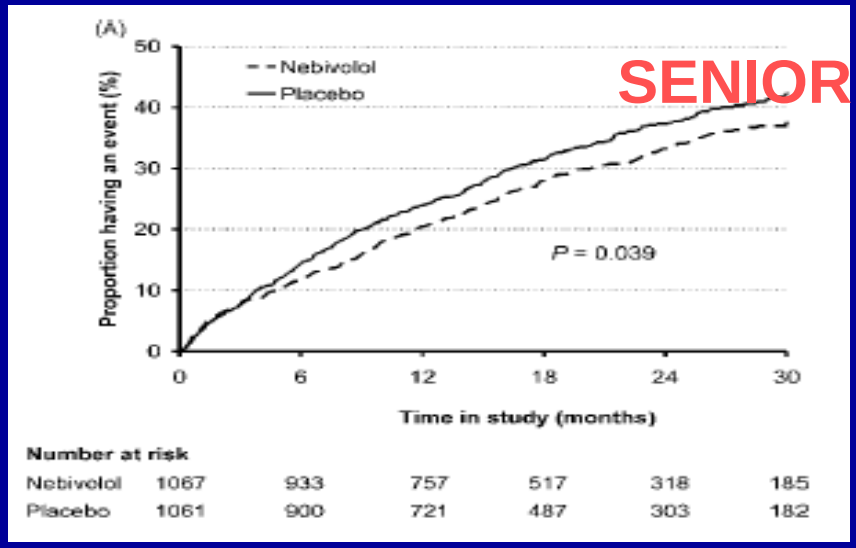
HR : Risk Factor? Or Marker?

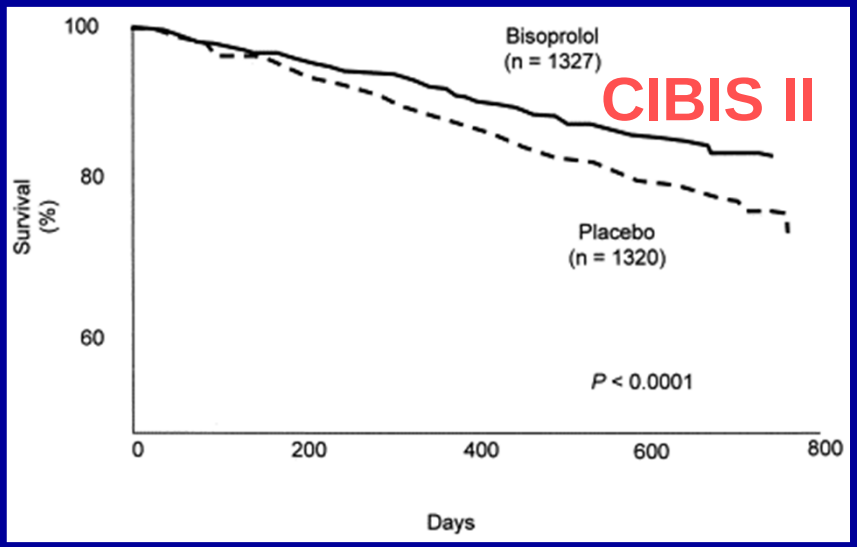
Trial	Agent	No. of patients	NYHA class	Mean follow-up (mo)	Annual placebo mortality rate (%)	Mortality risk reduction (%)	Target dose (mg)	Mean daily dose (mg)
CIBIS-II[6]	Bisoprolol	2647	III-IV	15	13.2	↓34	10 once daily	10[b]
MERIT-HF[7]	Metoprolol succinate	3991	II-IV	12	11.0	↓34	200 once daily	159
US carvedilol trials[9]	Carvedilol	1094	II-IV	6.5 (median)	7.8	↓65[c]	25-50 twice daily	45
ANZ[73]	Carvedilol	415	II-III	19	12.5	↓26	25 twice daily	41
COPERNICUS[74,75]	Carvedilol	2289	III-IV	10.4	19.7	↓35	25 twice daily	37
	Carvedilol	1511	II-IV	58	NR	↓27 (carvedilol vs metoprolol)	25 twice daily	41.8
COMET[76]	Metoprolol succinate	1518	II-IV	58	NR	NR	50 twice daily	85

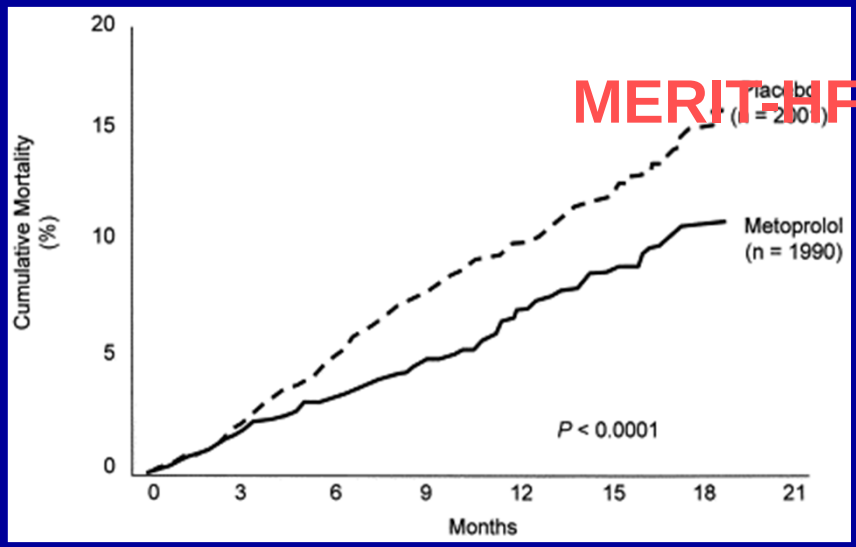
Evidence-based β-blocker	Initial dose (mg)	Maximal dose (mg)
Bisoprolol	1.25 once daily	10 once daily
Carvedilol[a]	3.125 twice daily	25 twice daily
Carvedilol controlled release	10.0 once daily	80 once daily
Metoprolol succinate	12.5-25.0 once daily	200 once daily

HR : Risk Factor? Or Marker?



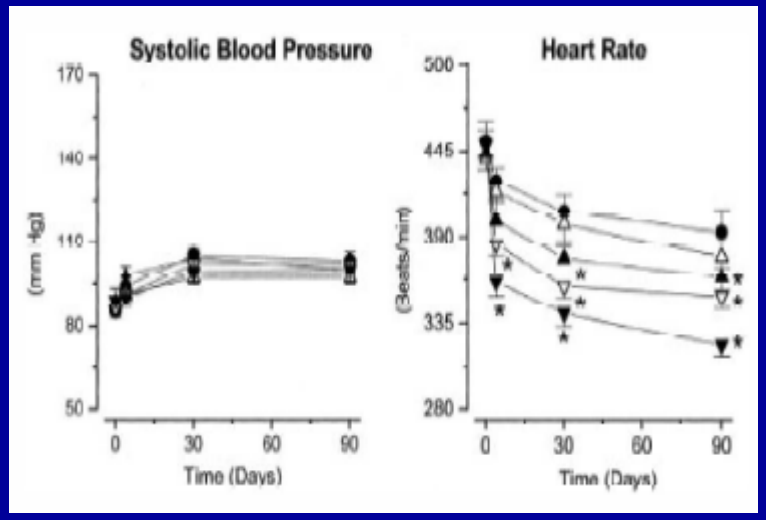


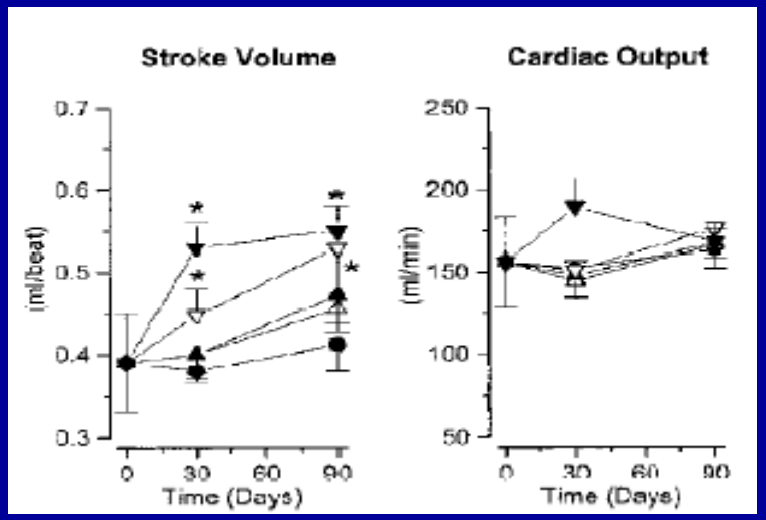




Ivabradine

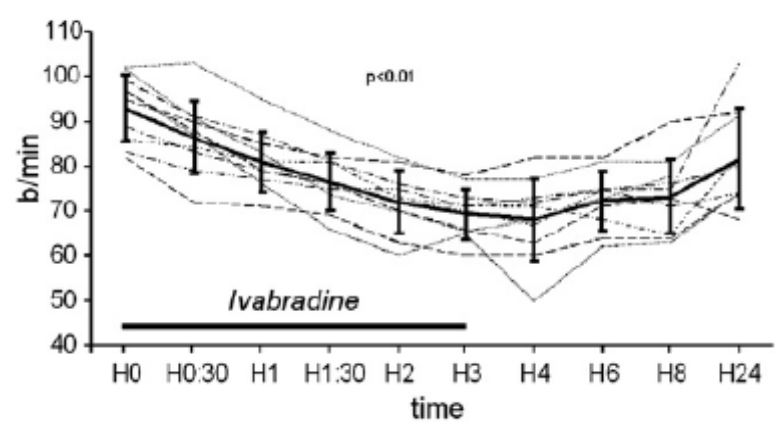
- Ivabradine, selective cardiac pacemaker I_f current inhibitor

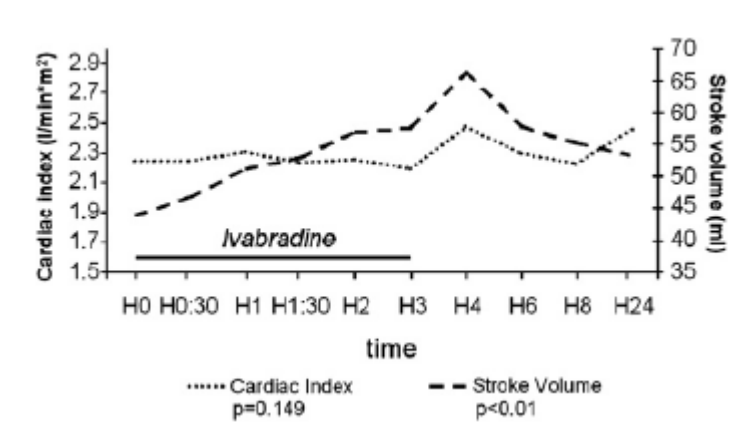




- This improvement in cardiac function is probably related not only to the HRR itself but also to modifications of LV structure and/or myocyte properties secondary to long-term HRR.

Ivabradine, Single-center trial





- ↓27% in HR with infusion of 0.15-0.175 mg/kg
- Importantly, this substantial HRR is ac preserved CO and significantly enhanced SV

Ivabradine, Multi-center trial

- Randomised, double-blind, placebo-controlled trials:

- Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfunction (BEAUTIFUL)

  - Kim F., et al. Lancet 2008;807-816

- The Systolic Heart Failure Treatment with the If Inhibitor Ivabradine Trial (SHIFT)

  - Swedberg K., et al. Lancet. 2011;376:875-85

BEAUTIFUL trial

- Addition of ivabradine to standard Tx. can reduce CV outcomes, Sx., QOL in HF with systolic dysfunction

- 10,917 Pts. Age > 55
  - CAD, LVEF < 40%, LVIDd > 56mm
  - Sinus rhythm, RHR > 60 bpm
  - Appropriate conventional medication
- Exclusion;
  - MI, revasc < 6M, Stroke, TIA<3 M
  - Pacemaker, cardioverter etc
  - SSS, AV block, etc / Severe HF (NYHA IV)

BEAUTIFUL trial

- Primary endpoint:

  Composite of CV death, admission due to AMI or new-onset or worsening HF

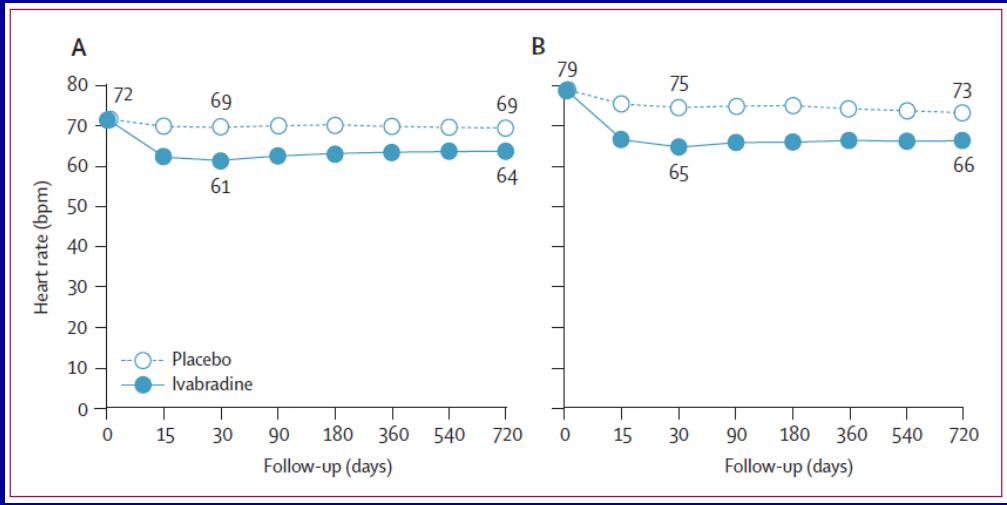
- Secondary endpoint:

  All cause mortality, Cardiac and CV death

  Admission due to AMI, UA

  Coronary revas. Admission due to HF or MI

BEAUTIFUL trial: Results



Mean HR

A. total study population

B. subgroup, HR>70bp,

	Ivabradine group (N=5477, 8893 patient-years)			Placebo group (N=5430, 8829 patient-years)			p value
	Events	Patients	Patient-years	Events	Patients	Patient-years	
All serious adverse events	1880	1233 (23%)	13·86	1975	1239 (23%)	14·03	0·70
Cardiac disorders	399	331 (6%)	3·72	403	324 (6%)	3·67	0·87
Infections and infestations	251	228 (4%)	2·56	261	218 (4%)	2·47	0·70
Nervous system disorders	220	205 (4%)	2·31	243	221 (4%)	2·50	0·38
Benign, malignant, and unspecified neoplasms (including cysts and polyps)	123	120 (2%)	1·35	137	135 (3%)	1·53	0·31
Vascular disorders	123	115 (2%)	1·29	129	113 (2%)	1·28	0·95
Gastrointestinal disorders	133	123 (2%)	1·38	117	109 (2%)	1·23	0·39
Respiratory, thoracic, and mediastinal disorders	83	73 (1%)	0·82	117	103 (2%)	1·17	0·02
Injury and poisoning	72	70 (1%)	0·79	74	60 (1%)	0·68	0·41
Renal and urinary disorders	75	66 (1%)	0·74	58	47 (1%)	0·53	0·08
Investigations	60	60 (1%)	0·67	69	65 (1%)	0·74	0·62
Metabolism and nutrition disorders	58	56 (1%)	0·63	61	58 (1%)	0·66	0·82
Musculoskeletal, connective-tissue, and bone disorders	55	53 (1%)	0·60	53	45 (1%)	0·51	0·44
Eye disorders	23	21 (0·4%)	0·24	12	12 (0·2%)	0·14	0·12
Blood and lymphatic system disorders	22	21 (0·4%)	0·24	28	24 (0·4%)	0·27	0·63
Psychiatric disorders	18	17 (0·3%)	0·19	7	5 (0·1%)	0·06	0·01
General disorders and administration-site conditions	12	12 (0·2%)	0·13	19	18 (0·3%)	0·20	0·26
Skin and subcutaneous-tissue disorders	10	10 (0·2%)	0·11	18	17 (0·3%)	0·19	0·17
Reproductive system and breast disorders	9	9 (0·2%)	0·10	23	21 (0·4%)	0·24	0·03

Serious adverse events are given for all 10 907 patients who had at least one dose of study drugs. The webtable shows all adverse events in more than 2% of patients.

Table 3: Incidence of serious adverse events during the study by system organ class

BEAUTIFUL trial: Results

	Total study population (N=10 917)				Prespecified subgroup with heart rate of 70 bpm or greater (N=5392)			
	Ivabradine group (N=5479)	Placebo group (N=5438)	HR (95% CI)	p value	Ivabradine group (N=2699)	Placebo group (N=2693)	HR (95% CI)	p value
Primary composite endpoint								
Cardiovascular death* or admission to hospital for myocardial infarction or new-onset or worsening heart failure†	844 (15·4%)	832 (15·3%)	1·00 (0·91–1·10)	0·94	463 (17·2)	498 (18·5)	0·91 (0·81–1·04)	0·17
Mortality endpoints								
All-cause death	572 (10·4%)	547 (10·1%)	1·04 (0·92–1·16)	0·55	331 (12·3)	324 (12·0)	1·02 (0·87–1·19)	0·82
Cardiovascular death*	469 (8·6%)	435 (8·0%)	1·07 (0·94–1·22)	0·32	269 (10·0)	263 (9·8)	1·02 (0·86–1·21)	0·82
Cardiac death‡	136 (2·5%)	151 (2·8%)	0·89 (0·71–1·12)	0·33	82 (3·0)	97 (3·6)	0·84 (0·62–1·12)	0·24
Heart failure endpoints								
Admission to hospital for heart failure†	426 (7·8%)	427 (7·9%)	0·99 (0·86–1·13)	0·85	268 (9·9)	271 (10·1)	0·97 (0·82–1·15)	0·76
Cardiovascular death* or admission to hospital for new-onset or worsening heart failure†	757 (13·8%)	723 (13·3%)	1·04 (0·94–1·15)	0·48	436 (16·2)	442 (16·4)	0·97 (0·85–1·11)	0·71
Coronary endpoints								
Admission to hospital for myocardial infarction*†	199 (3·6%)	226 (4·2%)	0·87 (0·72–1·06)	0·16	85 (3·1)	131 (4·9)	0·64 (0·49–0·84)	0·001
Admission to hospital for myocardial infarction† or unstable angina	303 (5·5%)	317 (5·8%)	0·95 (0·81–1·11)	0·50	143 (5·3)	182 (6·8)	0·78 (0·62–0·97)	0·023
Coronary revascularisation	155 (2·8%)	186 (3·4%)	0·83 (0·67–1·02)	0·078	76 (2·8)	108 (4·0)	0·70 (0·52–0·93)	0·016

Data are numbers of events (%), hazard ratios (HR) and 95% CIs, and p values. *Cardiac death, vascular procedure death, presumed arrhythmic death, stroke death, other vascular death, or sudden death of unknown cause. †Admission to hospital for myocardial infarction or heart failure includes fatal and non-fatal events. ‡Death from myocardial infarction, heart failure, or cardiac procedures.

Table 4: **Primary and secondary endpoints**

Did not affect Primary Endpoint

In subgroup(HR>70), reduce Secondary Endpoint

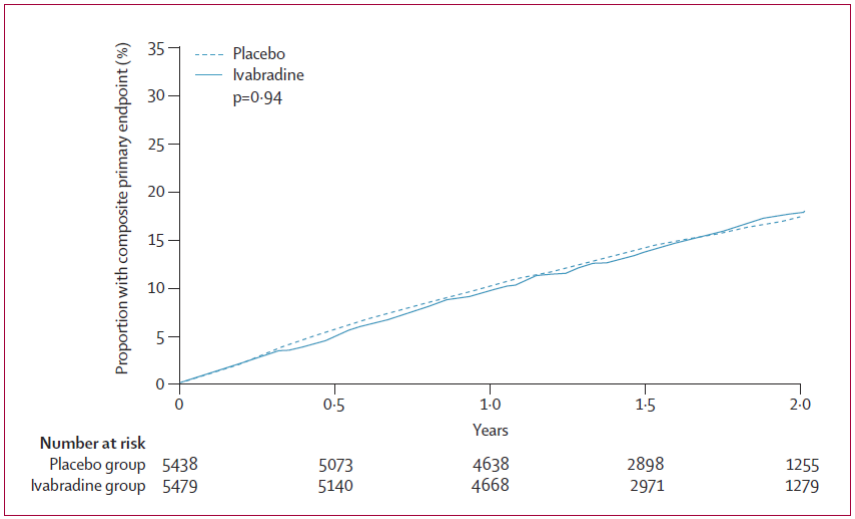
BEAUTIFUL trial: Results

Total study population, N=10,917

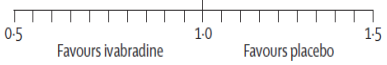
	Ivabradine group (N=5479)	Placebo group (N=5438)	HR (95% CI)	p value
Primary composite endpoint				
Cardiovascular death* or admission to hospital for myocardial infarction or new-onset or worsening heart failure†	844 (15·4%)	832 (15·3%)	1·00 (0·91–1·10)	0·94
Mortality endpoints				
All-cause death	572 (10·4%)	547 (10·1%)	1·04 (0·92–1·16)	0·55
Cardiovascular death*	469 (8·6%)	435 (8·0%)	1·07 (0·94–1·22)	0·32
Cardiac death‡	136 (2·5%)	151 (2·8%)	0·89 (0·71–1·12)	0·33
Heart failure endpoints				
Admission to hospital for heart failure†	426 (7·8%)	427 (7·9%)	0·99 (0·86–1·13)	0·85
Cardiovascular death* or admission to hospital for new-onset or worsening heart failure†	757 (13·8%)	723 (13·3%)	1·04 (0·94–1·15)	0·48
Coronary endpoints				
Admission to hospital for myocardial infarction*†	199 (3·6%)	226 (4·2%)	0·87 (0·72–1·06)	0·16
Admission to hospital for myocardial infarction† or unstable angina	303 (5·5%)	317 (5·8%)	0·95 (0·81–1·11)	0·50
Coronary revascularisation	155 (2·8%)	186 (3·4%)	0·83 (0·67–1·02)	0·078

BEAUTIFUL trial: Results

Total study population, N=10,917



	Ivabradine group	Placebo group	Hazard ratio	p value
β blockers				
No β blocker intake (N=1430)	144 (12·8%)	133 (12·3%)	1·04	
β blocker intake (N=9487)	700 (9·5%)	699 (9·5%)	1·00	0·763
Sex				
Female (N=1870)	152 (10·5%)	132 (9·2%)	1·14	
Male (N=9047)	692 (9·8%)	700 (10·0%)	0·98	0·226
Baseline heart rate				
<70 bpm (N=5525)	381 (8·7%)	334 (7·7%)	1·13	
≥70 bpm (N=5392)	463 (11·3%)	498 (12·3%)	0·91	0·030
Age				
<70 years (N=7657)	517 (8·6%)	530 (8·8%)	0·98	
≥70 years (N=3260)	327 (13·0%)	302 (12·7%)	1·02	0·681
Diabetes				
No history of diabetes (N=6881)	500 (9·2%)	463 (8·6%)	1·06	
History of diabetes (N=4036)	344 (11·3%)	369 (12·1%)	0·93	0·169
Metabolic syndrome				
No history of metabolic syndrome (N=6834)	533 (10·1%)	510 (9·6%)	1·05	
History of metabolic syndrome (N=4083)	311 (9·6%)	322 (10·3%)	0·93	0·257
Myocardial infarction				
No previous myocardial infarction (N=1272)	89 (9·0%)	98 (10·3%)	0·87	
Previous myocardial infarction (N=9645)	755 (10·0%)	734 (9·8%)	1·02	0·276
Revascularisation				
No previous revascularisation (N=5274)	470 (11·6%)	450 (11·4%)	1·02	
Previous revascularisation (N=5643)	374 (8·4%)	382 (8·5%)	0·98	0·740
Hypertension				
No history of hypertension (N=3197)	232 (9·1%)	233 (9·2%)	0·99	
History of hypertension (N=7720)	612 (10·3%)	599 (10·2%)	1·01	0·884
Heart failure				
NYHA class I and II heart failure (N=8385)	544 (8·2%)	543 (8·1%)	1·00	
NYHA class III heart failure (N=2532)	300 (16·2%)	289 (16·5%)	0·98	0·779
Ejection fraction				
Left-ventricular ejection fraction ≥35% (N=5118)	275 (6·7%)	291 (7·2%)	0·93	
Left-ventricular ejection fraction <35% (N=5791)	569 (13·0%)	541 (12·4%)	1·05	0·247



BEAUTIFUL trial: Results

Total study population, N=10,917

β blockers				
No β blocker intake (N=1430)	144 (12·8%)	133 (12·3%)	1·04	
β blocker intake (N=9487)	700 (9·5%)	699 (9·5%)	1·00	0·763
Baseline heart rate				
<70 bpm (N=5525)	381 (8·7%)	334 (7·7%)	1·13	
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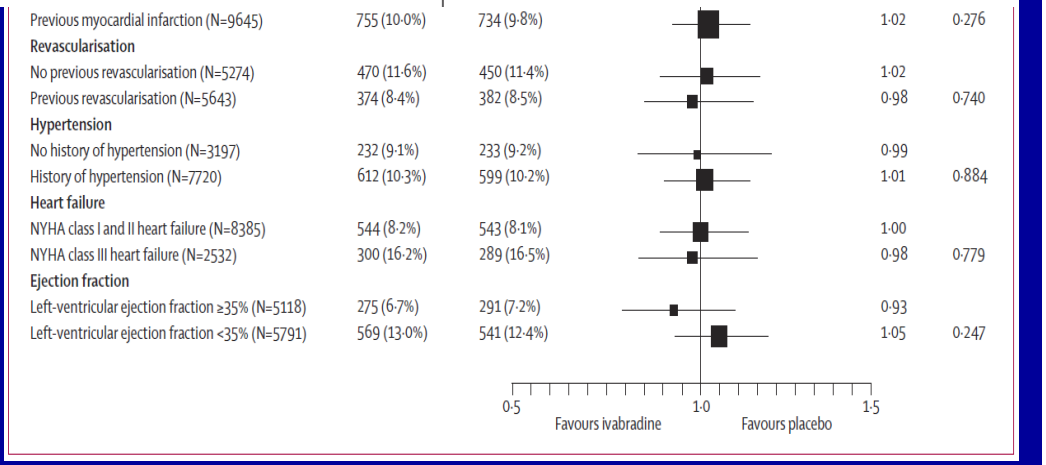


BEAUTIFUL trial: Results

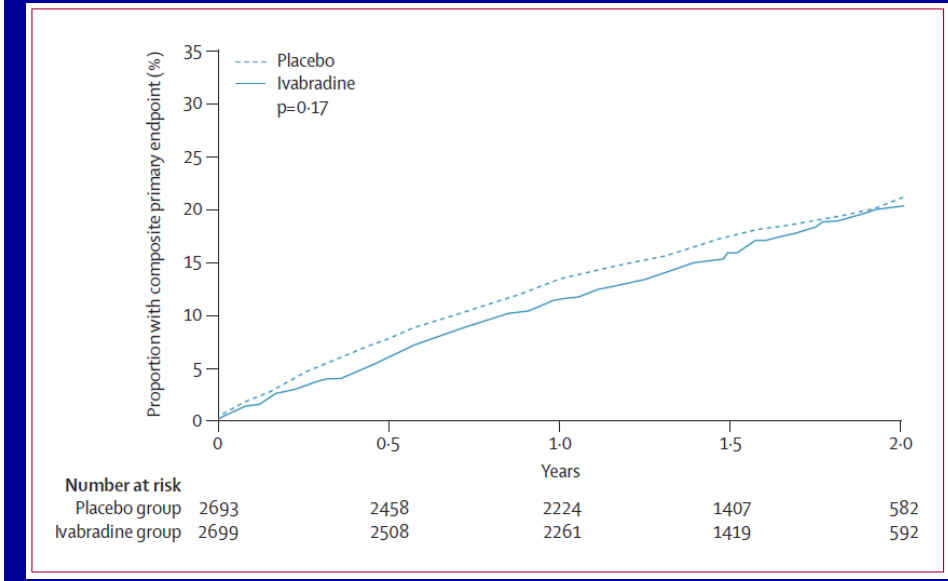
Subgroup, HR > 70 bpm, n=5392

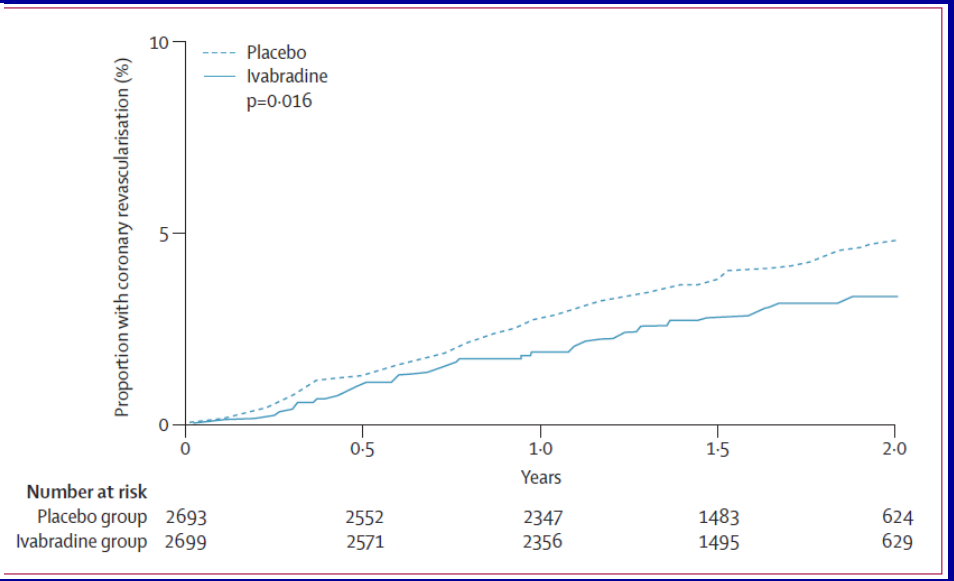
	Ivabradine group (N=2699)	Placebo group (N=2693)	HR (95% CI)	p value
Primary composite endpoint				
Cardiovascular death* or admission to hospital for myocardial infarction or new-onset or worsening heart failure†	463 (17·2)	498 (18·5)	0·91 (0·81–1·04)	0·17
Mortality endpoints				
All-cause death	331 (12·3)	324 (12·0)	1·02 (0·87–1·19)	0·82
Cardiovascular death*	269 (10·0)	263 (9·8)	1·02 (0·86–1·21)	0·82
Cardiac death‡	82 (3·0)	97 (3·6)	0·84 (0·62–1·12)	0·24
Heart failure endpoints				
Admission to hospital for heart failure†	268 (9·9)	271 (10·1)	0·97 (0·82–1·15)	0·76
Cardiovascular death* or admission to hospital for new-onset or worsening heart failure†	436 (16·2)	442 (16·4)	0·97 (0·85–1·11)	0·71
Coronary endpoints				
Admission to hospital for myocardial infarction*†	85 (3·1)	131 (4·9)	0·64 (0·49–0·84)	0·001
Admission to hospital for myocardial infarction† or unstable angina	143 (5·3)	182 (6·8)	0·78 (0·62–0·97)	0·023
Coronary revascularisation	76 (2·8)	108 (4·0)	0·70 (0·52–0·93)	0·016

BEAUTIFUL trial: Results

Subgroup, HR > 70 bpm, n=5392

Primary vs. Secondary endpoint



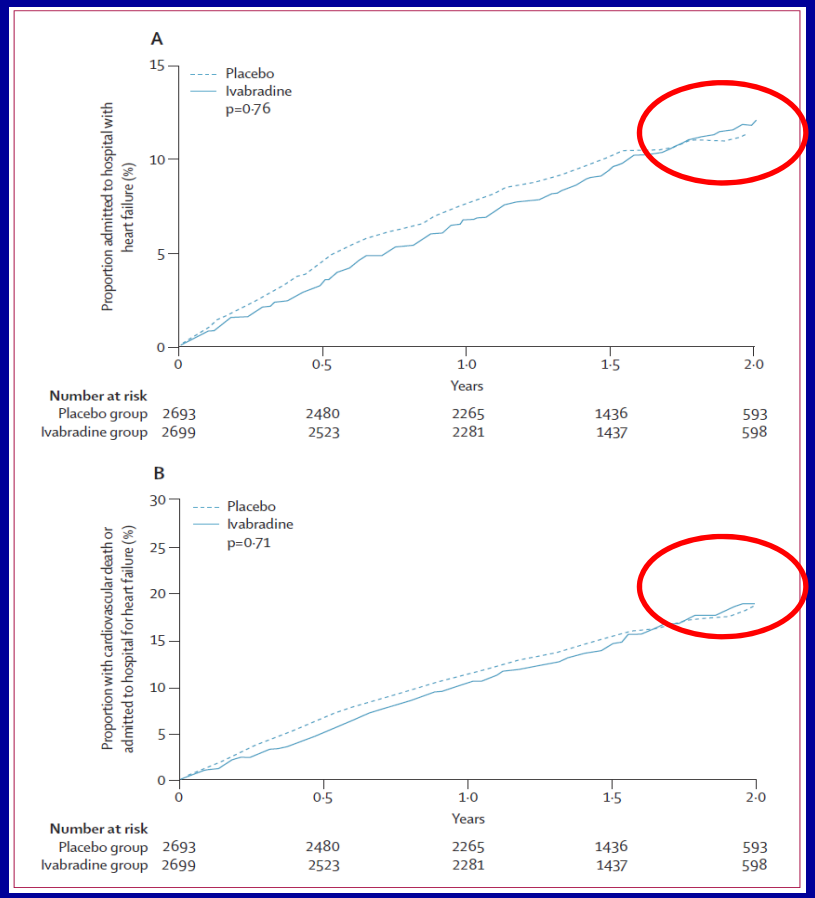


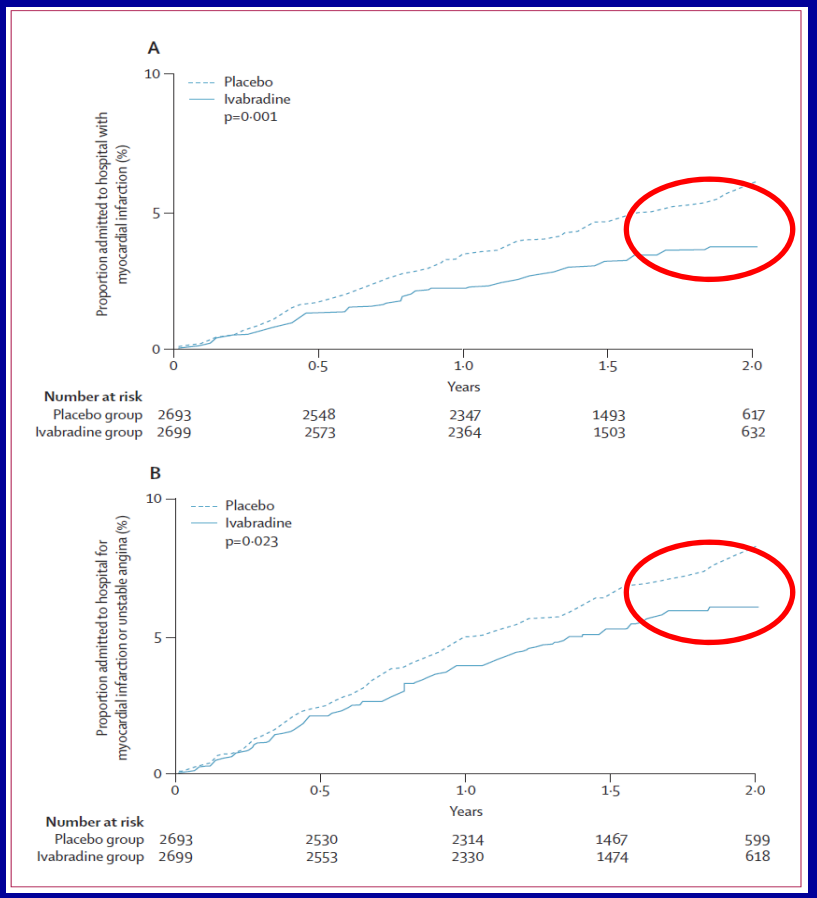
BEAUTIFUL trial: Results

Subgroup, HR > 70 bpm, n=5392

Heart Failure vs. Coronary endpoint

required HRR might differ according to underlying Dz.





BEAUTIFUL trial: Conclusions

- Interpretation:

  Reduction in HR with ivabradine does not improve cardiac outcome in all patients with stable CAD and LV systolic dysfunction.

- Can be given safely to CAD and LV dysfunction, and can be used in conjunction with beta-blockers
- Combination with beta-blcoker was not only safe but also improve CAD outcomes in patients with HR 70 bpm or more

SHIFT trial

- Ivabradine and outcomes in chronic heart failure (SHIFT): a randomised placebo-controlled study

  – Swedberg K., et al. Lancet. 2011;376:875-885

- HR as a risk factor in chronic heart failure (SHIFT): the association between HR and outcomes in a randomised placebo-controlled study

  – Bohm M., et al. Lancet. 2011;376:886-894

SHIFT trial (I): Outcomes in HF

- Ivabradine, in addition to guidelines-based Tx. on CV outcomes, Sx, QoL in CHF with systolic dysfunction
- 6,558 Pts. Age > 18, 22.9 Mon.

Main inclusion criteria

- NYHA Class II, III, or IV for ≥4 weeks, in stable clinical condition for ≥4 weeks
- Optimized and unchanged chronic heart failure medications and dosages for ≥4 weeks
- Hospital admission for worsening heart failure within previous 12 months
- Sinus rhythm with resting heart rate ≥70 b.p.m.
- Left-ventricular systolic dysfunction, with ejection fraction ≤35%, documented within previous 3 months

SHIFT trial

Main exclusion criteria

- Recent (<2 months) myocardial infarction or recent or scheduled coronary revascularization
- Severe primary valvular disease
- Scheduled surgery of valvular heart disease
- Stroke or transient cerebral ischaemia within previous 4 weeks
- Active myocarditis
- Congenital heart diseases
- On list for cardiac transplantation
- Cardiac resynchronization therapy started within previous 6 months
- Pacemaker with atrial or ventricular pacing (except biventricular pacing) >40% of the time, or with stimulation threshold at the atrial or ventricular level ≥60 b.p.m.
- Permanent atrial fibrillation or flutter
- Sick sinus syndrome, sinoatrial block, second and third degree atrio-ventricular block
- History of symptomatic or sustained (≥30 s) ventricular arrhythmia unless a cardioverter/defibrillator implanted
- Cardioverter/defibrillator shock within previous 6 months
- Family history or congenital long QT syndrome or treated with selected QT-prolonging products
- Severe or uncontrolled hypertension (SBP >180 mmHg or DBP > 110 mmHg)
- Sitting SBP <85 mmHg or current symptomatic hypotension
- Known moderate or severe liver disease, known severe renal disease or known anaemia

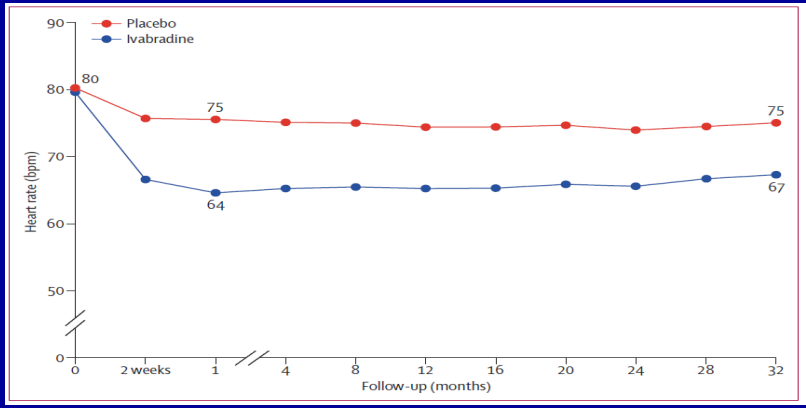
SHIFT trial

- Primary endpoint:
  Composite of CV death, admission due to worsening HF

- Secondary endpoint:
  Composite of CV death or admission for worsening HF in Pts. receiving at least 50% of target daily dose of beta-blocker.
  All cause, any CV death
  etc

SHIFT trial: Results

Mean HR



	Ivabradine group (n=3232)		Placebo group (n=3260)		p value
	Events	Patients with an event	Events	Patients with an event	
All serious adverse events	3388	1450 (45%)	3847	1553 (48%)	0·025
Cardiac disorders	1804	920 (28%)	2051	991 (30%)	0·091
General disorders and administration site conditions	242	240 (7%)	262	254 (8%)	0·607
Infection and infestations	268	216 (7%)	294	236 (7%)	0·381
Nervous system disorders	144	130 (4%)	202	178 (5%)	0·007
Respiratory, thoracic, and mediastinal disorders	153	107 (3%)	174	122 (4%)	0·347
Surgical and medical procedures	117	102 (3%)	130	122 (4%)	0·197
Gastrointestinal disorders	101	89 (3%)	116	103 (3%)	0·342
Neoplasm (benign, malignant, and unspecified)	70	68 (2%)	66	61 (2%)	0·534
Renal and urinary disorders	59	51 (2%)	51	47 (1%)	0·685
Hepatobiliary disorders	30	29 (1%)	44	39 (1%)	0·273
Eye disorders	24	18 (1%)	15	13 (<1%)	0·374

Data are number of events or number of patients (%). Patients included in this safety analysis are those who had taken at least one dose of study drug. p values are calculated on the basis of number of patients.

Table 4: **Incidence of relevant serious adverse events during the study by system organ class**

SHIFT trial: Results

Primary Endpoint: HR 0.82 (0.75–0.90, p<0.0001)

Mainly by admissions for worsening HF, deaths due to HF

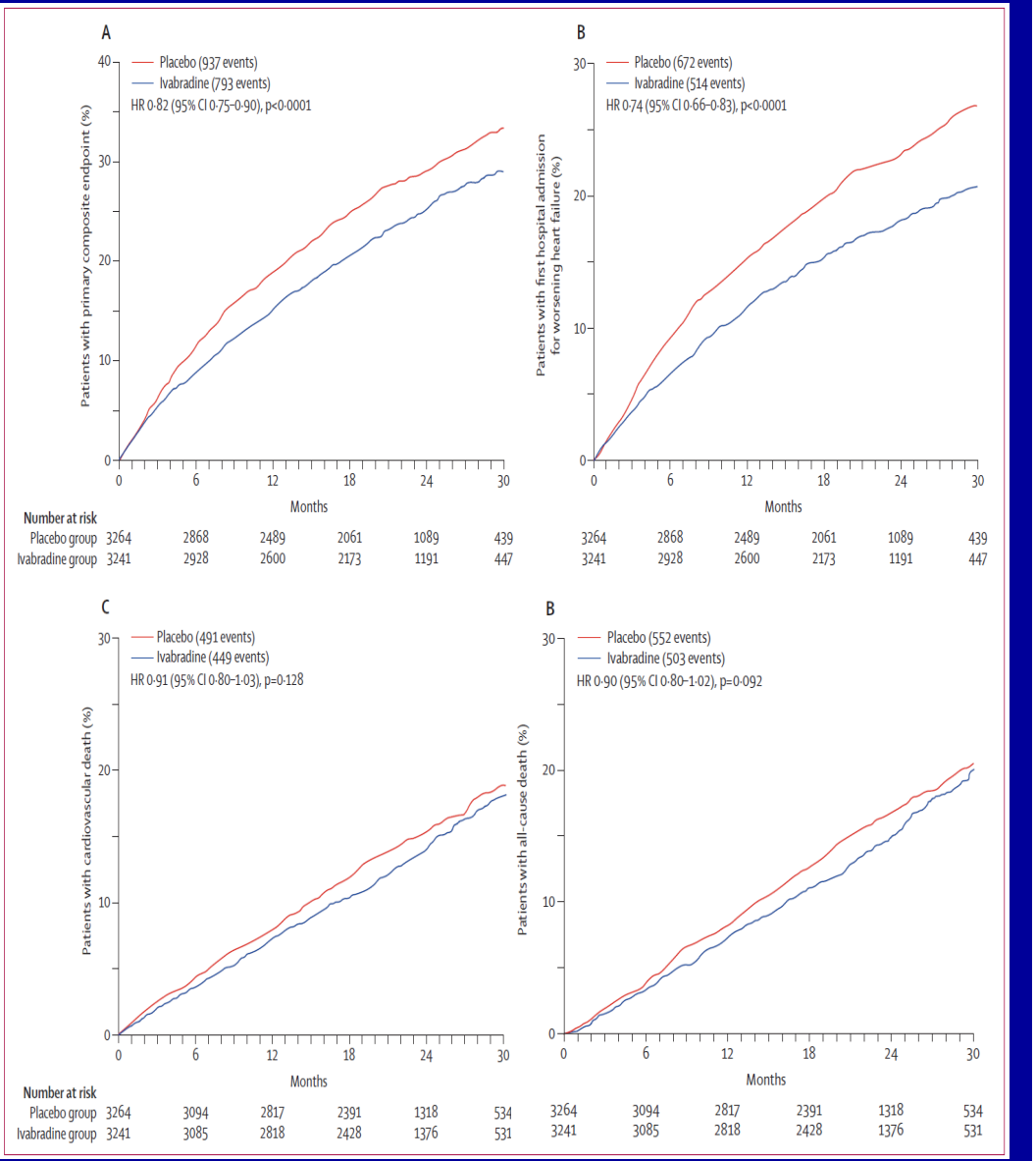
	Ivabradine group (n=3241)	Placebo group (n=3264)	HR (95% CI)	p value
Primary endpoint				
Cardiovascular death or hospital admission for worsening heart failure	793 (24%)	937 (29%)	0·82 (0·75–0·90)	<0·0001
Mortality endpoints				
All-cause mortality	503 (16%)	552 (17%)	0·90 (0·80–1·02)	0·092
Cardiovascular mortality	449 (14%)	491 (15%)	0·91 (0·80–1·03)	0·128
Death from heart failure	113 (3%)	151 (5%)	0·74 (0·58–0·94)	0·014
Other endpoints				
All-cause hospital admission	1231 (38%)	1356 (42%)	0·89 (0·82–0·96)	0·003
Hospital admission for worsening heart failure	514 (16%)	672 (21%)	0·74 (0·66–0·83)	<0·0001
Any cardiovascular hospital admission	977 (30%)	1122 (34%)	0·85 (0·78–0·92)	0·0002
Cardiovascular death, or hospital admission for worsening heart failure, or hospital admission for non-fatal myocardial infarction	825 (25%)	979 (30%)	0·82 (0·74–0·89)	<0·0001

Data are number of first events (%), hazard ratio (HR; 95% CI), and p values.

Table 3: **Effects on primary and major secondary endpoints**

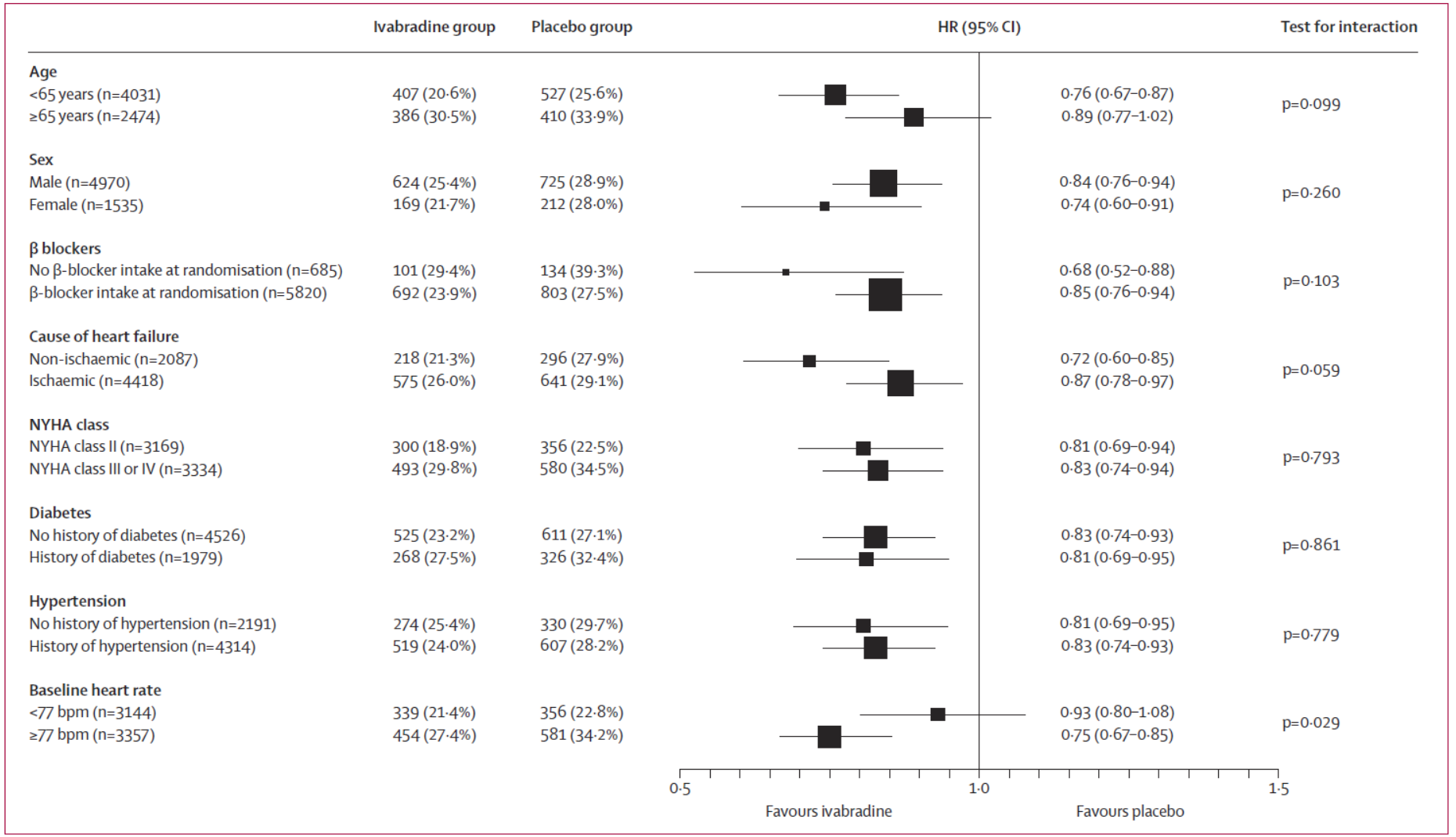
SHIFT trial: Results

A. Primary composite endpoint of CV death or admission for worsening HF
   HR 0.82 (0.75–0.90, p<0.0001)
B. Admission for worsening HF
C. CV death
D. All cause death



SHIFT trial: Results

Effect on Pri. composite endpoint in prespecified subgroups



SHIFT(I) trial: Conclusions

- Interpretation:

Our results support the importance of HR-reduction with ivabradine for improvement of clinical outcomes in HF and confirm the important role of HR in the pathophysiology of this disorder.

BEAUTIFUL(Subgroup) vs. SHIFT trial

BEAUTIFUL Trial Investigators

Executive Committee: K Fox (Chair), R Ferrari, I Ford, P G Steg, M Tendera. *Steering Committee*: R Ferrari (Chair), H Grancelli (Argentina), B Freedman (Australia), B Eber (Austria), J L Vanoverschelde (Belgium), B Finkov, Y Yotov (Bulgaria), J C Tardif (Canada), D Hu (China), C Lau (Hong Kong), J Hradec (Czech Republic), P Hildebrandt (Denmark), J Eha (Estonia), K Peuhkurinen (Finland), N Danchin, P G Steg (France), T Meinertz (Germany), P Vardas (Greece), J Borbola (Hungary), D Mulcahy (Ireland), A Maggioni (Italy), A Erglis, J Jirgensons,† U Kalnins† (Latvia), A Laucevicius (Lithuania), K Dickstein (Norway), W Ruzyllo, M Tendera (Poland), R Seabra-Gomes (Portugal), R Capalneanu (Romania), Y Belenkov, Y Mareev (Russia), J Murin (Slovakia), P Rakovec (Slovenia), C Macaya (Spain), M Dellborg (Sweden), T U Lüscher (Switzerland), W van Gilst (Netherlands), A Oto (Turkey), I Ford, K Fox, A Hall (UK), A Parkhomenko (Ukraine)

SHIFT trial committees

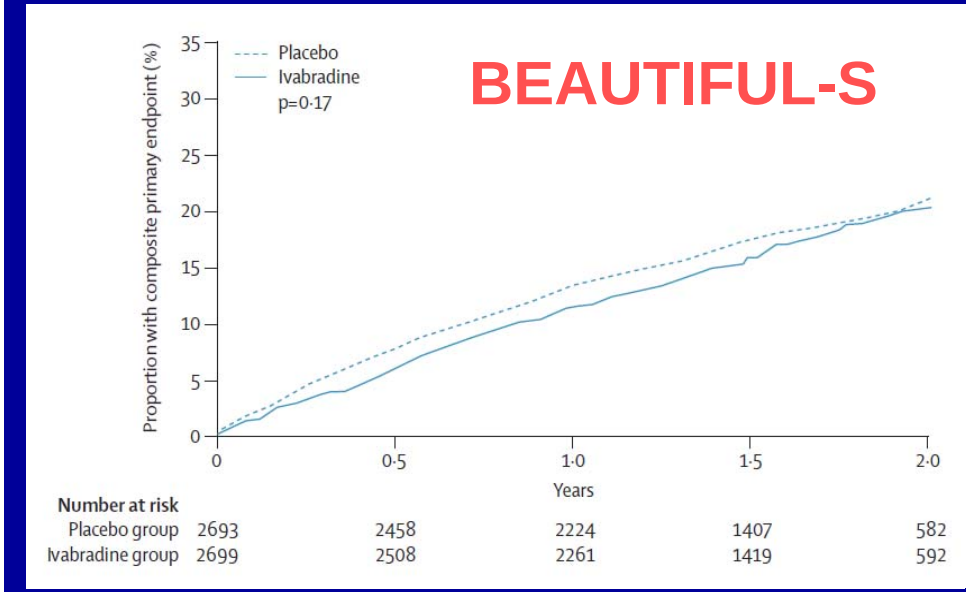
Executive committee: Karl Swedberg (co-chair), Michel Komajda (co-chair), Luigi Tavazzi, Jeffrey S Borer, Michael Böhm, Ian Ford, Ariane Dubost-Brama (non-voting), Guy Lerebours (non-voting). *Steering committee:* S Perrone (Argentina), H Krum (Australia), W Van Mieghem (Belgium), E A Bocchi (Brazil), T Katova (Bulgaria), P Liu (Canada), J Jalil (Chile), D Hu (China), J Vitovec (Czech Republic), L Køber (Denmark), T Uuetoa (Estonia), M Niemela (Finland), G Jondeau (France), K Werdan (Germany), D Kremastinos (Greece), C M Yu (Hong Kong), K Toth (Hungary), D Seshagiri Rao (India), K McDonald (Ireland), M Metra (Italy), B H Oh (South Korea), J Jirgenson (deceased), A Erglis (Latvia), A Kavoluniene (Lithuania), K H Sim (Malaysia), A A Voors (The Netherlands), K Dickstein (Norway), G Opolski (Poland), L Providencia (Portugal), D D Ionescu (Romania), G Aroutiounov (Russia), R Hatala (Slovakia), M Sebestjen (Slovenia), F Aviles (Spain), R Willenheimer (Sweden), A Oto (Turkey), M Cowie (UK), O Parkhomenko (Ukraine). *Endpoint validation committee:* J L Lopez-Sendon (Chair, Spain), K Dickstein (Norway), P Ponikowski (Poland), A Gavazzi (Italy), E Lopez de Sa (Spain), J R Gonzalez Juanatey (Spain), A M W Alings (The Netherlands).

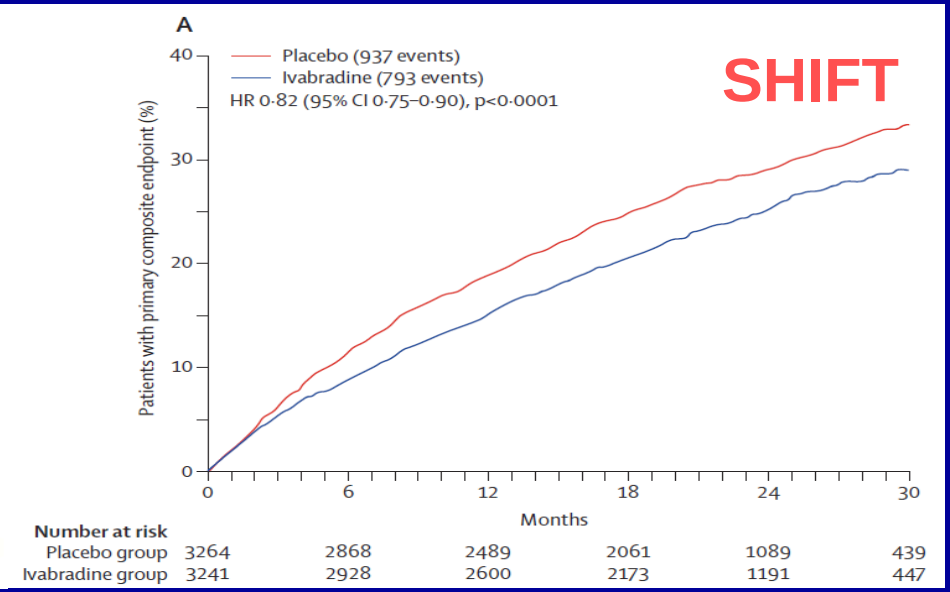
BEAUTIFUL(Subgroup) vs. SHIFT trial

Primary composite endpoint:

Composite of CV death, admission due to AMI or new-onset or worsening HF vs.

Composite of CV death, admission due to worsening HF

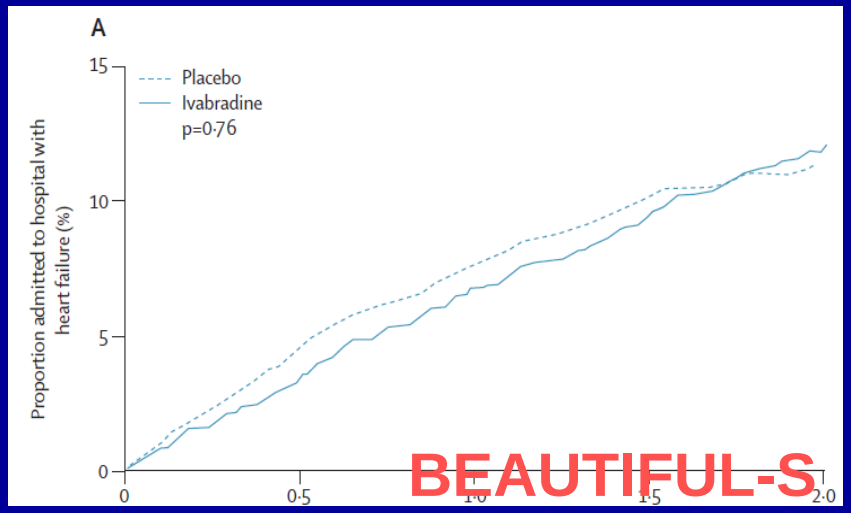




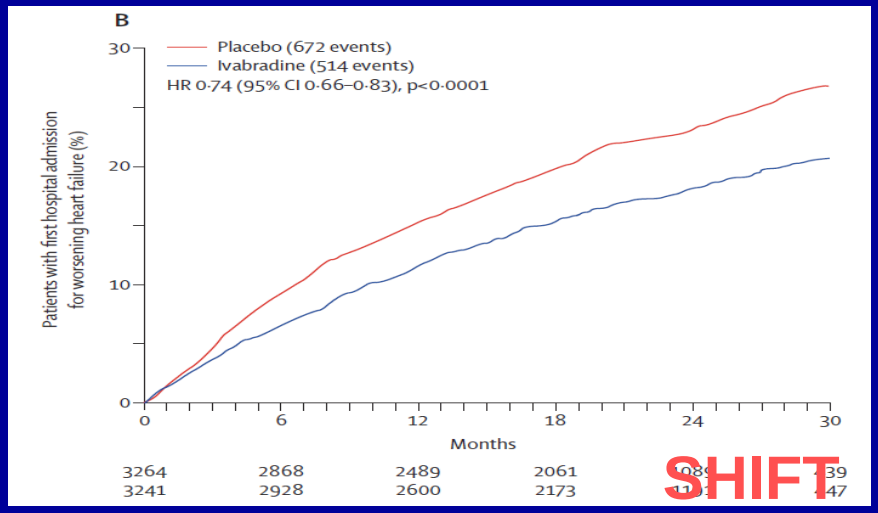
BEAUTIFUL(Subgroup) vs. SHIFT trial

Adm(A) or CV death or adm.(B) for new-onset or worsening HF

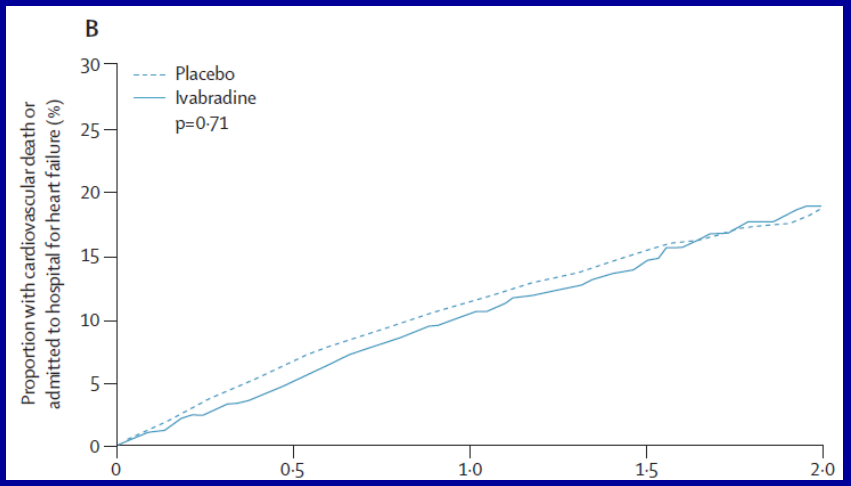
Adm(B) for worsening HF
CV death(C)

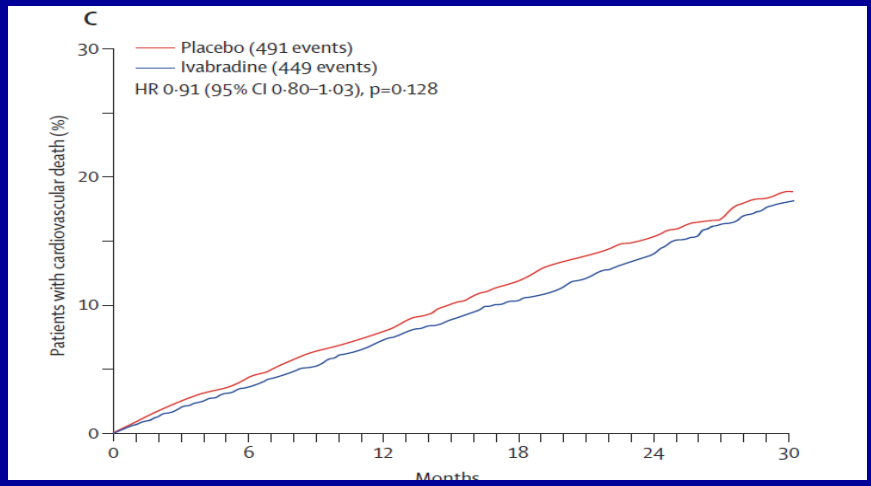


BEAUTIFUL-S



SHIFT





BEAUTIFUL(Subgroup) vs. SHIFT trial

	Ivabradine group (n=2699)	Placebo group (n=2693)	Subgroup (N=5392)
Demographic characteristics			
Age (years)	64·8 (8·6)	64·4 (8·6)	64·6 (8·6)
Sex (male)	2206 (82%)	2209 (82%)	4415 (82%)
Smoking (current)	432 (16%)	481 (18%)	913 (17%)
Body-mass index (kg/m²)	28·8 (4·6)	28·7 (4·7)	28·8 (4·6)
Medical history			
History of hypertension	1947 (72%)	1927 (72%)	3874 (72%)
History of diabetes	1132 (42%)	1155 (43%)	2287 (42%)
History of dyslipidaemia	2119 (79%)	2123 (79%)	4242 (79%)
Previous myocardial infarction	2355 (87%)	2349 (87%)	4704 (87%)
Previous percutaneous coronary intervention or coronary artery bypass graft	1333 (49%)	1360 (51%)	2693 (50%)
Previous stroke	501 (19%)	503 (19%)	1004 (19%)
Peripheral artery disease	373 (14%)	402 (15%)	775 (14%)
Cardiac parameters			
Heart rate (bpm)	79·1 (8·5)	79·2 (8·7)	79·2 (8·6)
Systolic blood pressure (mm Hg)	128·9 (15·9)	128·5 (15·7)	128·7 (15·8)
Diastolic blood pressure (mm Hg)	78·4 (9·4)	78·3 (9·2)	78·3 (9·3)
Left-ventricular ejection fraction (%)	32·0 (5·6)	31·9 (5·7)	32·0 (5·6)
NYHA class I heart failure	389 (14%)	373 (14%)	762 (14%)
NYHA class II heart failure	1575 (58%)	1615 (60%)	3190 (59%)
NYHA class III heart failure	735 (27%)	705 (26%)	1440 (27%)
Medication at randomisation			
Aspirin or antithrombotic agent	2536 (94%)	2507 (93%)	5043 (94%)
Statin	1941 (72%)	1945 (72%)	3886 (72%)
Angiotensin-converting enzyme inhibitor, angiotensin II receptor blocker, or both	2411 (89%)	2421 (90%)	4832 (90%)
β blocker	2233 (83%)	2273 (84%)	4506 (84%)
Organic nitrates	1161 (43%)	1202 (45%)	2363 (44%)
Diuretics (excluding antialdosterone)	1691 (63%)	1704 (63%)	3395 (63%)
Antialdosterone agents	792 (29%)	800 (30%)	1592 (30%)

Data are number (%) or mean (SD). NYHA=New York Heart Association.

Table 2: **Baseline characteristics of the subgroup with heart rate of 70 bpm or greater**

	Ivabradine group (n=3241)	Placebo group (n=3264)
Demographic characteristics		
Age (years)	60·7 (11·2)	60·1 (11·5)
Sex (male)	2462 (76%)	2508 (77%)
Ethnic origin		
White	2879 (89%)	2892 (89%)
Asian	268 (8%)	264 (8%)
Other	94 (3%)	108 (3%)
Current smoking	541 (17%)	577 (18%)
BMI (kg/m²)	28·0 (5·1)	28·0 (5·0)
Cardiac parameters		
Heart rate (bpm)	79·7 (9·5)	80·1 (9·8)
SBP (mm Hg)	122·0 (16·1)	121·4 (15·9)
DBP (mm Hg)	75·7 (9·6)	75·6 (9·4)
LVEF (%)	29·0% (5·1)	29·0% (5·2)
eGFR (mL/min per 1·73 m²)	74·6 (22·9)	74·8 (23·1)
NYHA class		
Class II	1585 (49%)	1584 (49%)
Class III	1605 (50%)	1618 (50%)
Class IV	50 (2%)	61 (2%)
Medical history		
Duration of heart failure (years)	3·5 (4·2)	3·5 (4·2)
Primary cause of heart failure		
Ischaemic	2215 (68%)	2203 (67%)
Non-ischaemic	1026 (32%)	1061 (33%)
Myocardial infarction	1829 (56%)	1837 (56%)
Hypertension	2162 (67%)	2152 (66%)
Diabetes	973 (30%)	1006 (31%)
Previous stroke	228 (7%)	295 (9%)
History of atrial fibrillation or flutter	263 (8%)	259 (8%)
Treatment at randomisation		
β blocker	2897 (89%)	2923 (90%)
ACE inhibitor	2565 (79%)	2551 (78%)
ARB	455 (14%)	472 (14%)
Diuretic drugs (excluding antialdosterone)	2719 (84%)	2695 (83%)
Antialdosterone agents	1981 (61%)	1941 (59%)
Cardiac glycosides	706 (22%)	710 (22%)
Devices	110 (3%)	134 (4%)
CRT	28 (1%)	44 (1%)
ICD	92 (3%)	115 (4%)

BEAUTIFUL-S vs. SHIFT trial

Demographic characteristics and Medication history

	BEAU.-S n=5392	SHIFT n=3241			
Demographic Characteristics			Medication History		
Age, Yr.	64.6	60.7	Aspirin, %	94	
Sex(M, %)	82	76	ACE +/- ARB, %	90	79/14
Smoking, %	17	17	Beta-blocker, %	84	89
BMI, kg/m2	28.8	28	target dose>50%		56
Inclusion Criteria			Antialdo. %	30	61
Resting HR	> 60 bpm	> 70 bpm	Diuretics, %	63	84
			Statin	72	
			CRT, ICD		1 /3

BEAUTIFUL-S vs. SHIFT trial

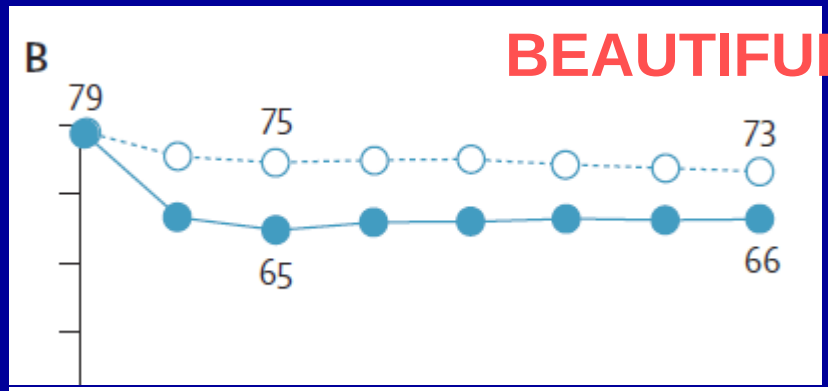
Medical History and Cardiac Parameters

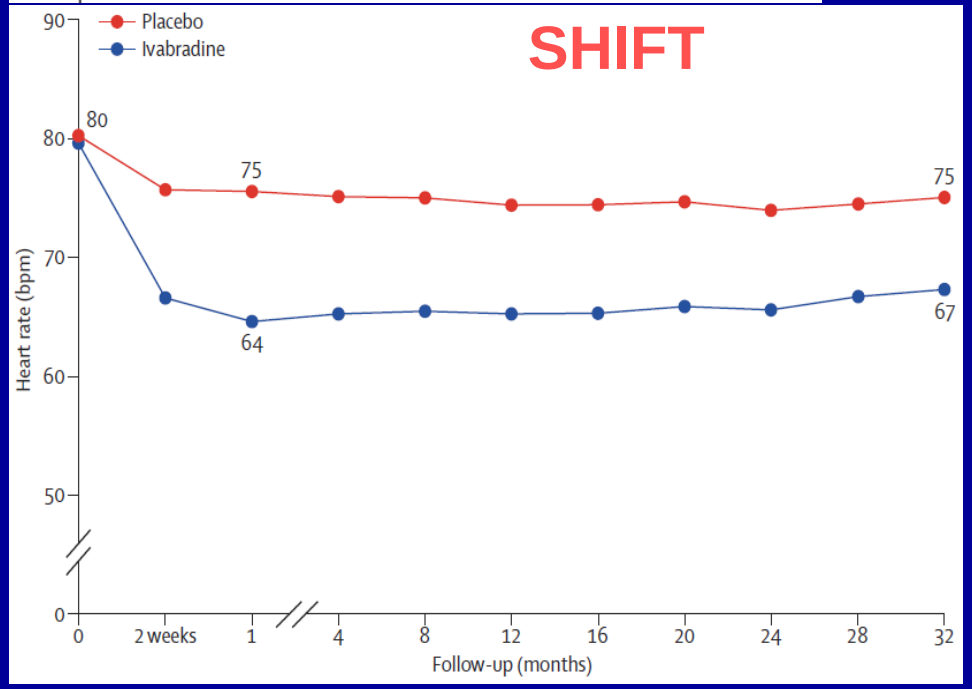
	BEAU.-S n=5392	SHIFT n=3241
Medical History		
HTN, %	72	67
DM, %	42	30
Stroke, %	19	7
MI, %	87	56
PCI, CABG,%	50	
Ischemic, %		67
Non-Isc., %		33

Cardiac parameters		
HR, bpm	79.2	79.7
SBP, mmHg	128.7	122
DBP, mmHg	78.3	75.7
LVEF, %	32	29
NYHA II, %	59	49
NYHA III, %	27	50

BEAUTIFUL(Subgroup) vs. SHIFT trial

Cardiac parameters and medication history





Dosage

6.18, bid at 1 mo.
(7.5bid, >40%)

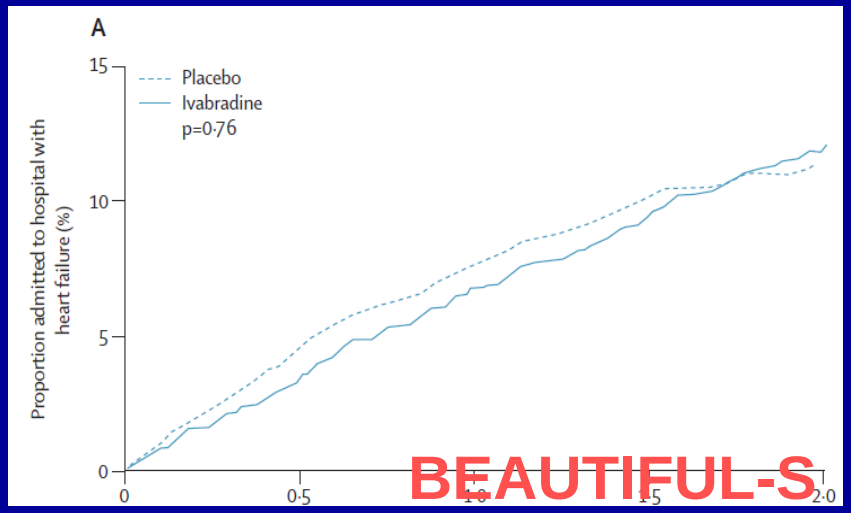
vs.

6.5,bid at 1 mo.

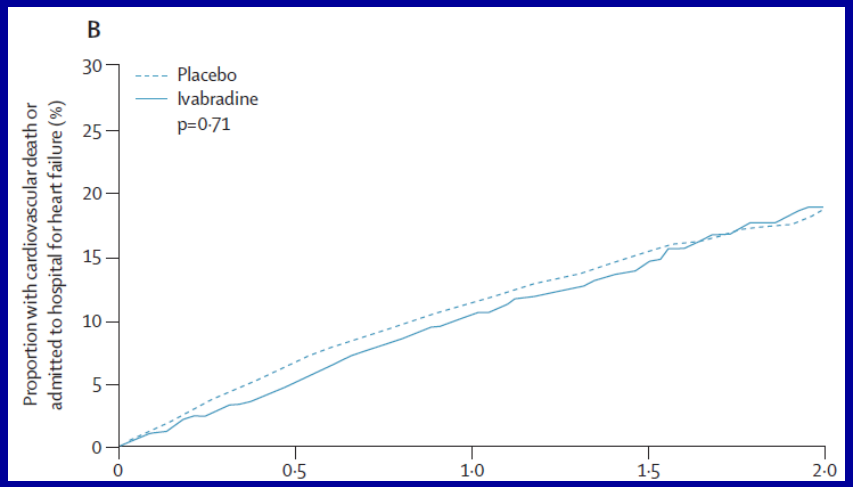
6.5 bid at 1Yr

BEAUTIFUL(Subgroup) vs. SHIFT trial

Adm(A) or CV death or adm.(B) for new-onset or worsening HF

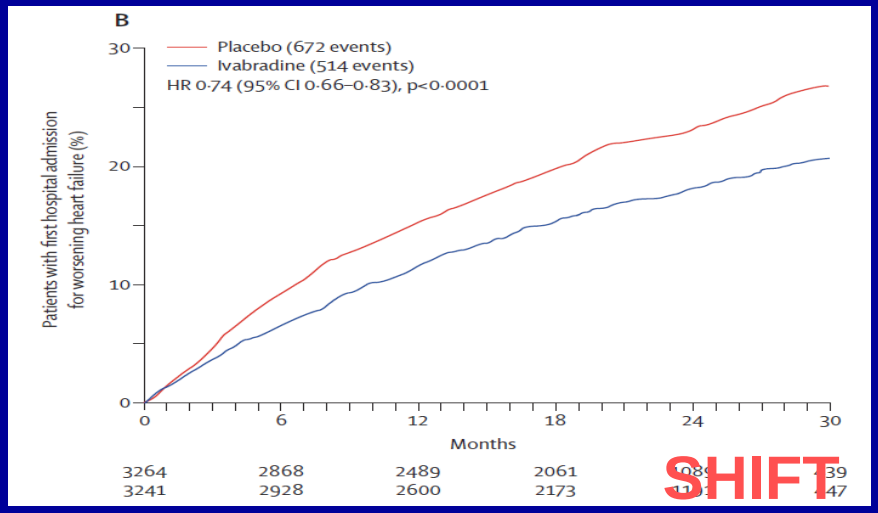


BEAUTIFUL-S

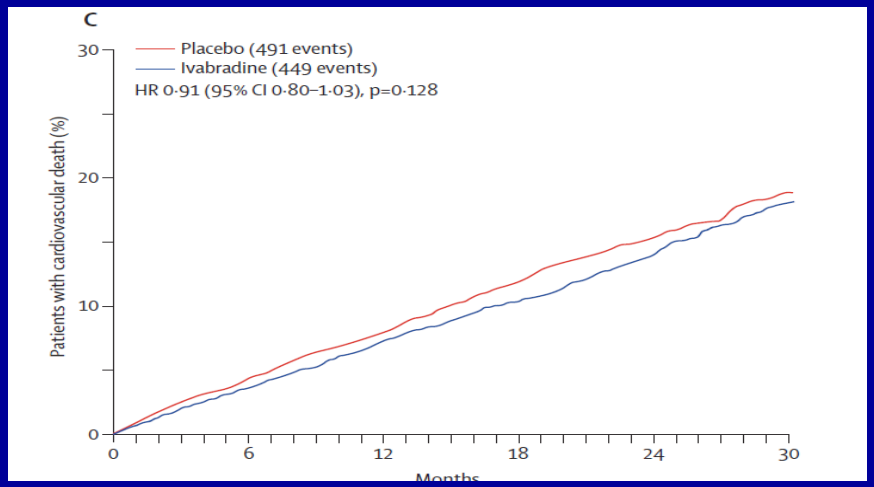


Adm(B) for worsening HF

CV death(C)



SHIFT



SHIFT trial (II): HR, Risk Factor in HF

- Analysed CV outcomes in both group, divided by quintiles of baseline HR(bpm):
- 70 – 72 – 75 – 80 – 87 <

Main inclusion criteria

- NYHA Class II, III, or IV for ≥4 weeks, in stable clinical condition for ≥4 weeks
- Optimized and unchanged chronic heart failure medications and dosages for ≥4 weeks
- Hospital admission for worsening heart failure within previous 12 months
- Sinus rhythm with resting heart rate ≥70 b.p.m.
- Left-ventricular systolic dysfunction, with ejection fraction ≤35%, documented within previous 3 months

SHIFT trial

	Heart-rate group at baseline					p value
	70 to <72 bpm (n=987)	72 to <75 bpm (n=1364)	75 to <80 bpm (n=1545)	80 to <87 bpm (n=1287)	≥87 bpm (n=1318)	
Demographic characteristics						
Age (years)	62·5 (11·1)	61·4 (11·0)	60·3 (11·4)	60·2 (11·3)	58·2 (11·7)	<0·0001
Sex (male)	752 (76%)	1028 (75%)	1193 (77%)	970 (75%)	1024 (78%)	0·495
Ethnic origin						
White	879 (89%)	1254 (92%)	1373 (89%)	1125 (87%)	1136 (86%)	0·0009
Asian	84 (9%)	78 (6%)	116 (8%)	115 (9%)	139 (11%)	..
Other	24 (2%)	32 (2%)	56 (4%)	47 (4%)	43 (3%)	..
Current smoking	147 (15%)	188 (14%)	248 (16%)	230 (18%)	305 (23%)	<0·0001
BMI (kg/m^2)	27·6 (4·5)	28·2 (4·9)	27·9 (5·0)	28·1 (5·1)	28·1 (5·6)	0·125
Cardiac parameters						
Heart rate (bpm)	70·4 (1·1)	72·9 (0·8)	76·6 (1·4)	82·4 (2·0)	95·6 (8·0)	..
SBP (mm Hg)	122·0 (15·4)	122·3 (15·0)	121·8 (16·0)	122·0 (16·4)	120·3 (16·7)	0·006
DBP (mm Hg)	74·8 (9·3)	75·9 (9·0)	75·5 (9·4)	75·7 (9·5)	76·2 (10·1)	0·027
LVEF (%)	29·8 (5·0)	29·6 (4·9)	29·0 (5·1)	29·0 (5·0)	27·8 (5·4)	<0·0001
eGFR (mL/min per 1·73 kg/m^2)	72·9 (21·9)	73·3 (22·6)	75·1 (22·6)	75·4 (23·9)	76·3 (23·5)	0·001

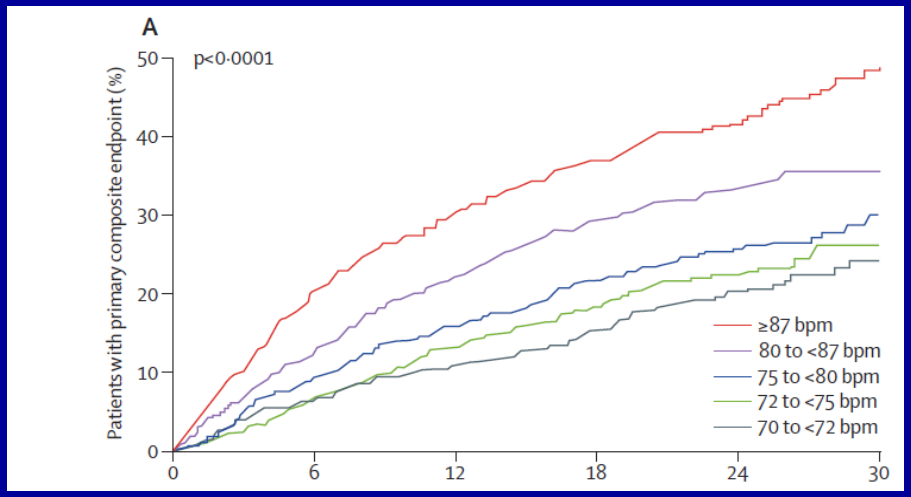
SHIFT trial

	Heart-rate group at baseline					p value
	70 to <72 bpm (n=987)	72 to <75 bpm (n=1364)	75 to <80 bpm (n=1545)	80 to <87 bpm (n=1287)	≥87 bpm (n=1318)	
NYHA class						
Class II	509 (52%)	708 (52%)	816 (53%)	615 (48%)	521 (40%)	<0·0001
Class III	466 (47%)	642 (47%)	710 (46%)	633 (49%)	768 (58%)	..
Class IV	12 (1%)	12 (1%)	19 (1%)	39 (3%)	29 (2%)	..
Medical history						
Duration of heart failure (years)	3·6 (4·3)	3·6 (4·5)	3·5 (4·3)	3·5 (4·0)	3·3 (3·8)	0·116
Primary cause of heart failure						
Ischaemic	728 (74%)	966 (71%)	1048 (68%)	865 (67%)	809 (61%)	<0·0001
Non-ischaemic	259 (26%)	398 (29%)	497 (32%)	422 (33%)	509 (39%)	..
Myocardial infarction	603 (61%)	800 (59%)	882 (57%)	721 (56%)	659 (50%)	<0·0001
Hypertension	679 (69%)	949 (70%)	1013 (66%)	848 (66%)	821 (62%)	0·0007
Diabetes	261 (26%)	413 (30%)	457 (30%)	409 (32%)	437 (33%)	0·008
Previous stroke	70 (7%)	121 (9%)	103 (7%)	115 (9%)	112 (8%)	0·084
History of atrial fibrillation and/or flutter	80 (8%)	122 (9%)	119 (8%)	107 (8%)	90 (7%)	0·344

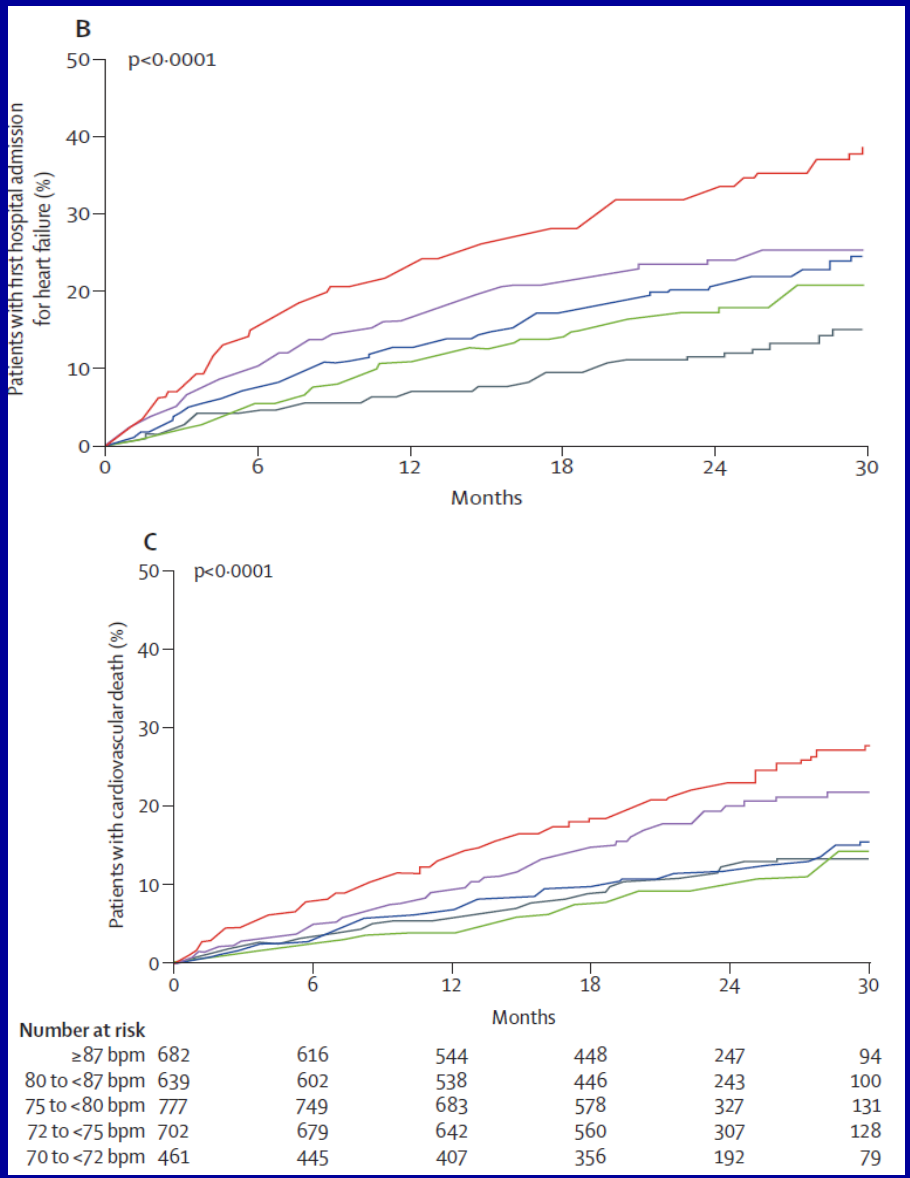
SHIFT trial

	Heart-rate group at baseline					p value
	70 to <72 bpm (n=987)	72 to <75 bpm (n=1364)	75 to <80 bpm (n=1545)	80 to <87 bpm (n=1287)	≥87 bpm (n=1318)	
Treatment at randomisation						
β blocker	919 (93%)	1258 (92%)	1422 (92%)	1138 (88%)	1079 (82%)	<0·0001
ACE inhibitors	795 (81%)	1102 (81%)	1244 (81%)	979 (76%)	993 (75%)	0·0001
ARBs	126 (13%)	199 (15%)	208 (13%)	203 (16%)	190 (14%)	0·271
Diuretic agents (excluding antialdosterone)	804 (81%)	1122 (82%)	1261 (82%)	1088 (85%)	1135 (86%)	0·004
Antialdosterone agents	551 (56%)	810 (60%)	915 (59%)	783 (61%)	859 (65%)	0·0001
Cardiac glycosides	175 (18%)	249 (18%)	319 (21%)	300 (23%)	371 (28%)	<0·0001
Devices						
CRT	8 (1%)	12 (1%)	16 (1%)	13 (1%)	23 (2%)	0·164
ICD	25 (3%)	45 (3%)	51 (3%)	44 (3%)	41 (3%)	0·783

SHIFT trial: Results



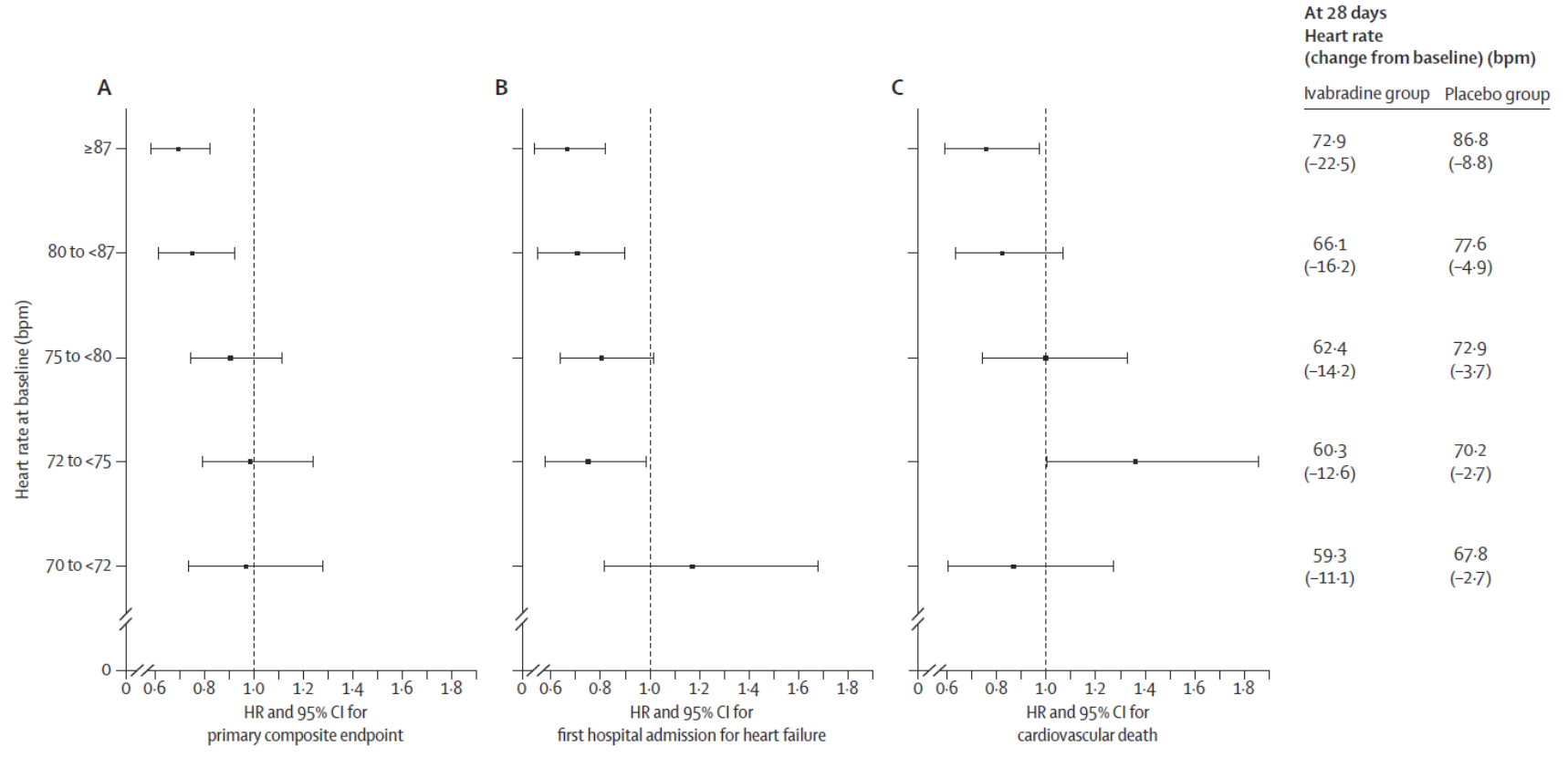
- (A) Primary composite endpoint
- (B) First hospital adm. for worsening HF
- (C) Cardiovascular deaths in placebo group



Number at risk						
≥87 bpm	682	616	544	448	247	94
80 to <87 bpm	639	602	538	446	243	100
75 to <80 bpm	777	749	683	578	327	131
72 to <75 bpm	702	679	642	560	307	128
70 to <72 bpm	461	445	407	356	192	79

SHIFT trial: Results

- Effect of ivabradine compared with placebo:



(A) Primary composite endpoint, (B) First hospital admission for worsening HF, (C) Cardiovascular deaths

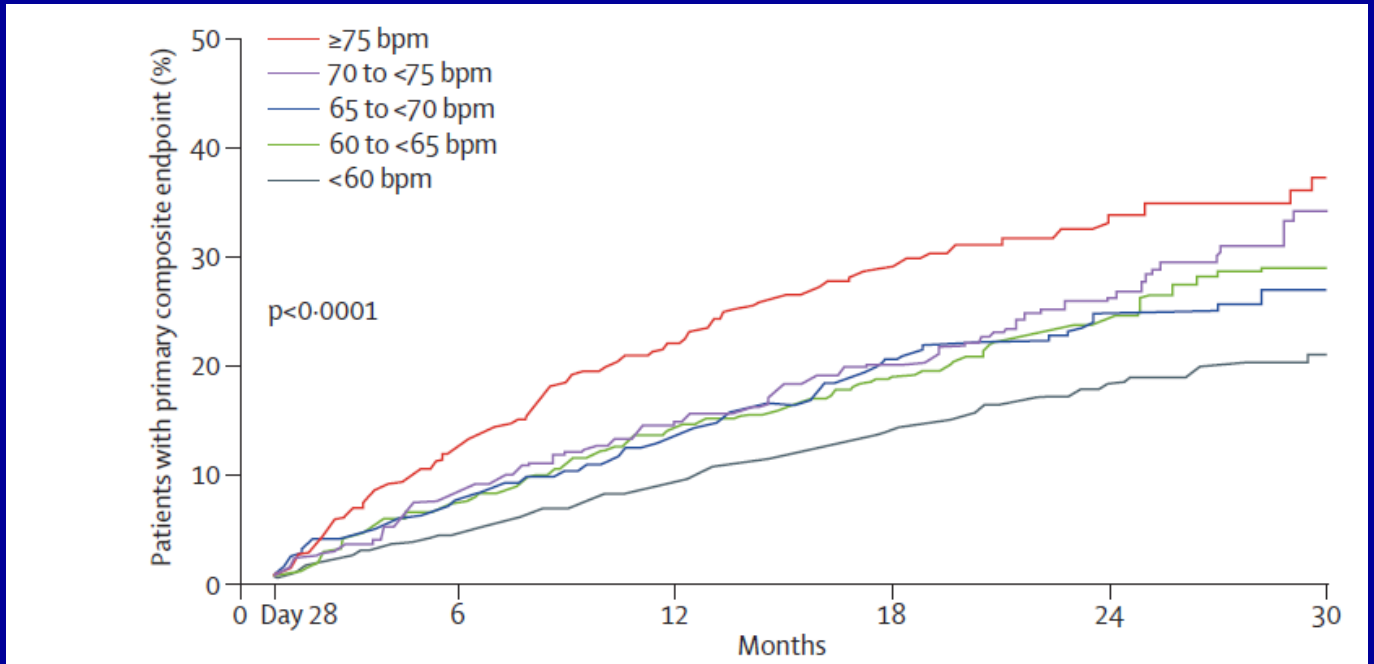
SHIFT trial: Results

- Effect of ivabradine compared with placebo:

The Hazard ration for the effects of ivabradine relative to placebo, adjusted for progrnostic factors and for change of heart rate at 28 days, was 0.95(CI, 0.85-1.06, p=0.362).

SHIFT trial: Results

- Primary composite endpoint according to HR achieved at 28days, in ivabradine group



Number at risk						
≥75 bpm	527	451	376	291	141	47
70 to <75 bpm	344	314	276	221	116	41
65 to <70 bpm	444	404	358	287	149	62
60 to <65 bpm	605	556	488	407	176	59
<60 bpm	1192	1132	1004	842	414	162

SHIFT(II) trial: Conclusions

- Interpretation:

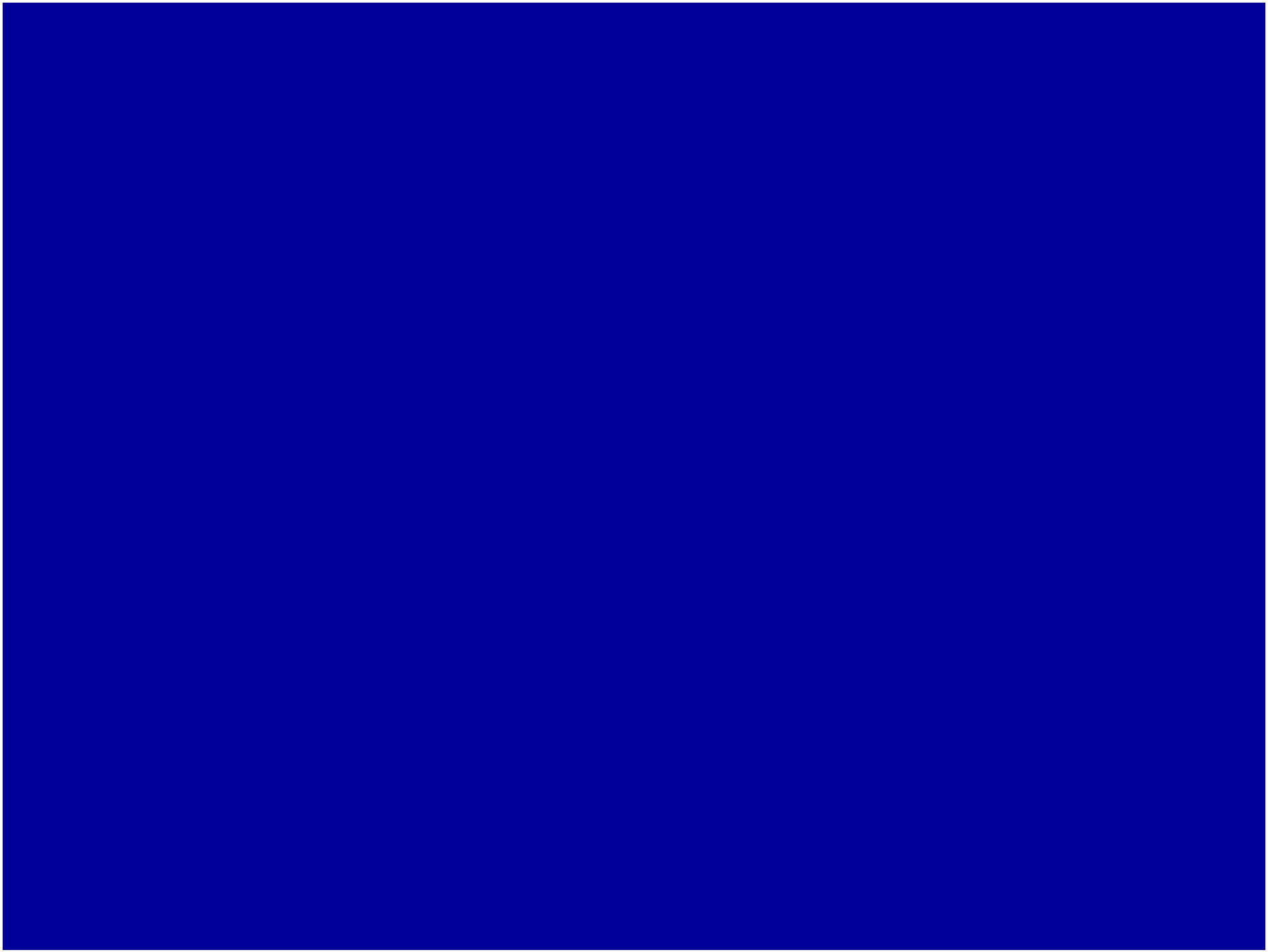
Our analysis confirm that high HR is a risk factor in HF. Selective lowering of HR with ivabradine improves cardiovascular outcomes. Heart rate is an important target for treatment of heart failure

- Risk of CV outcome increases with HR
- 16% risk in primary outcome/5 bpm
- The beneficial effect neutralized for subsequent outcomes after adjustment for change in HR at 28 days

In Summary,

- Clinical implications of SHIFT trial is:

- Greater attention to simple biomarker, Resting Heart Rate
- Ivabradine should be considered, remained elevated HR despite of beta-blocker
- May be substitute beta-blocker(?)
- No clear answer according to co-prescription
- Not generalized to overall HF population such as AF, LBBB



HR Modulation: SHIFT or Not to SHIFT

- Ivabradine,

  Selective cardiacpacemaker(I_f)inhibitor
- Enhanced HR:

  If Risk factor, Traget HR?
- Up-titration of Beta-Blocker?
- Co-prescription with Ivabradine?
- Substitute?

HR Modulation

- SHIFT trial,
- Not-confirmative, on-going trial
- B-blocker, 89%
  56%, >50% of target dose (26% TDose)
- ACE-Inhibitor, ARB, 79/14%
- Aldosterone antagonist, 61%
  (NYHA III/IV, 52%)
- Most white, BMI 28.0 kg/m2
- Not generalized to CHF, Afib. LBBB
- Long-term efficacy

HR Modulation

- SHIFT trial,
- B-blocker, > 50% of target dose
  - Despite 15.5 bpm reduction in RHR
  - Not achieve Pri-EP (0.77-1.04, p=0.155)
  - Not modified mortality component
  - Event rate for primary outcome was lower than overall population(13%/Yr)

Up-titration of Beta-blocker is Important

Limited role for Ivabradine in Tx of CHF

- 2211 Pts, LVEF<50%
- Suitability: LVEF<35%, SR with RHR>70 bpm
  19.4% at baseline (n=429)
  14.1% at 4 months (n=185)
  9 % at 12 months (n=82)
  5.2% (n=48), NYHA-I +/- no BB excluded

- After up-titration of HF medications, the number of patients 'suitable' for ivabradine therapy was small.

  - Cullungton D, et al. Heart. 2011:97;1961-6

Target Dose vs. Target HR of B-Blocker

- 210 of 600 Pts. Retrospective analysis
- Hx. Of HF (Ischemic or Non-ischemic)
- Stable dose of BB at least 3 Mo.
- Target Dose:

  carvedilol >50 mg, bisoprolol 10mg,

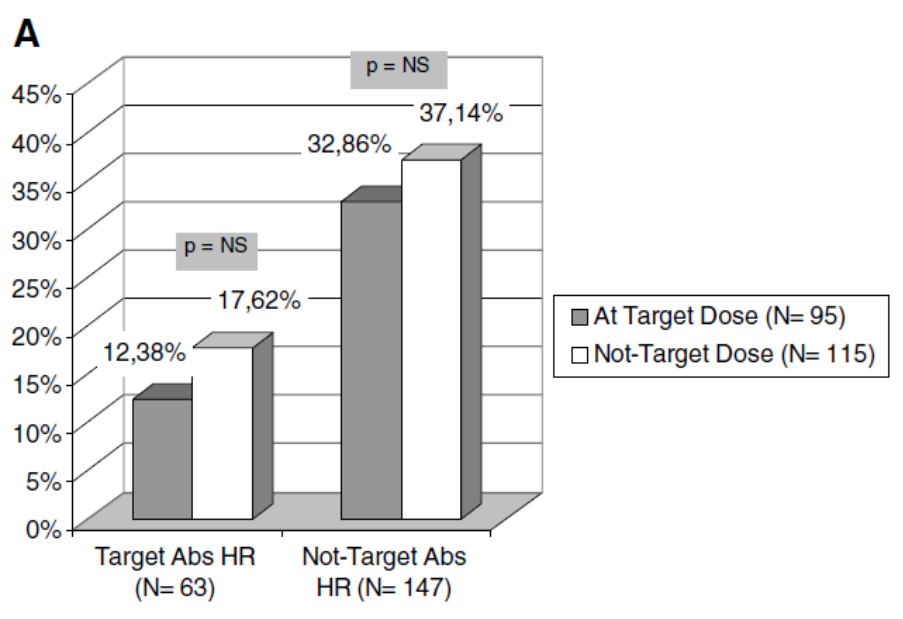
  metoprolol 190 mg daily
- Target HR:

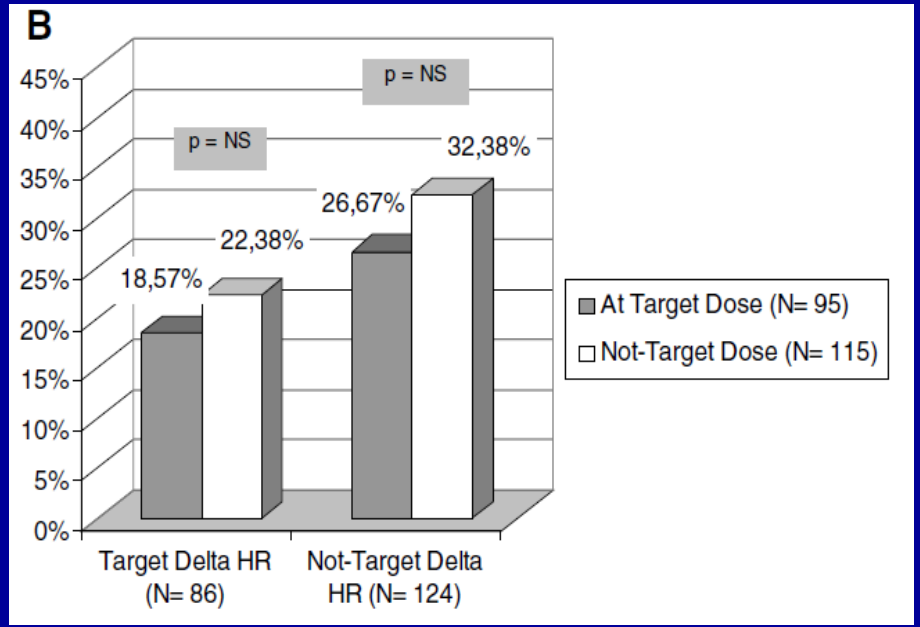
  < 60 bpm, HR-Change>10 bpm

- Porapakkham P, et al Cardiovasc Ther. 2010;28(2);93-100

Target Dose vs. Target HR of B-Blocker

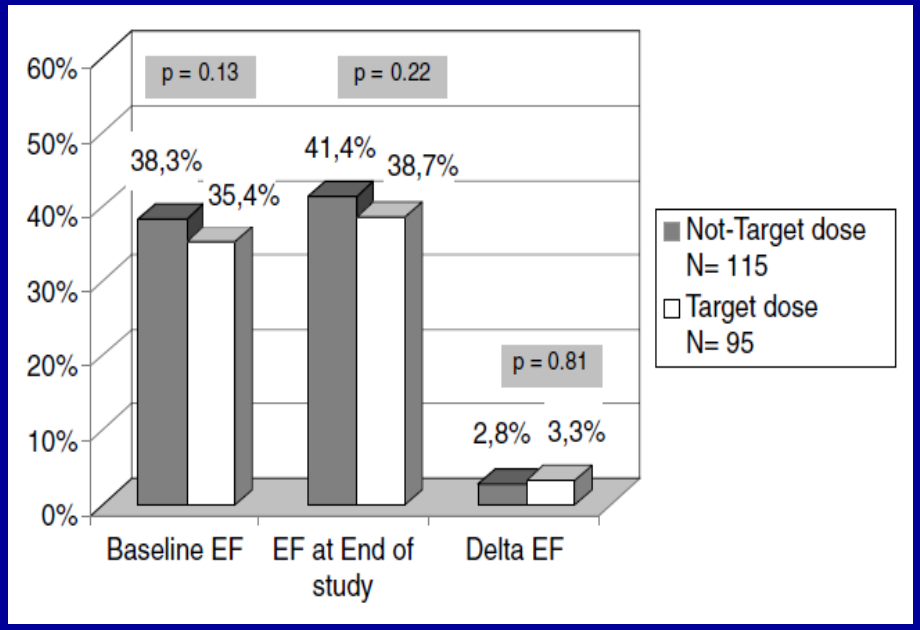
Target Dose vs. (A) target absolute HR(60bpm),
(B) target delta HR(10bpm)





Target Dose vs. Target HR of B-Blocker

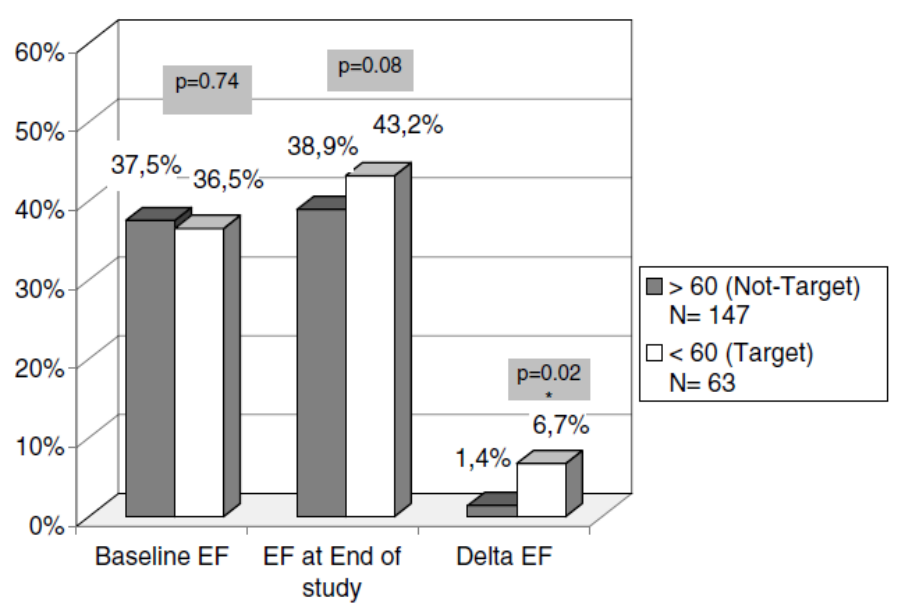
Target Dose vs. absolute EF

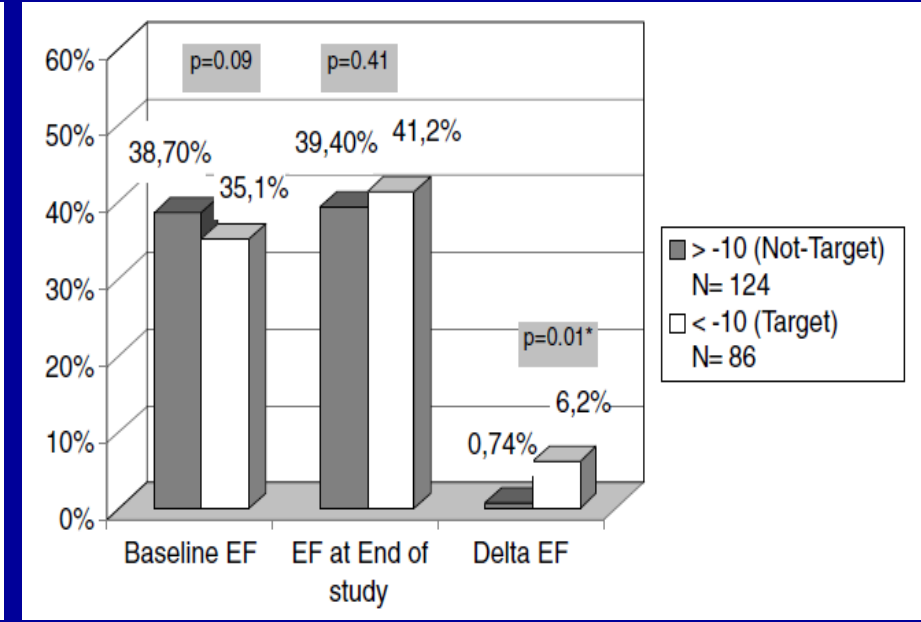


Target Dose vs. Target HR of B-Blocker

Target absolute HR vs. absolute EF

Target Delta HR





HR Reduction on Clinical Outcome

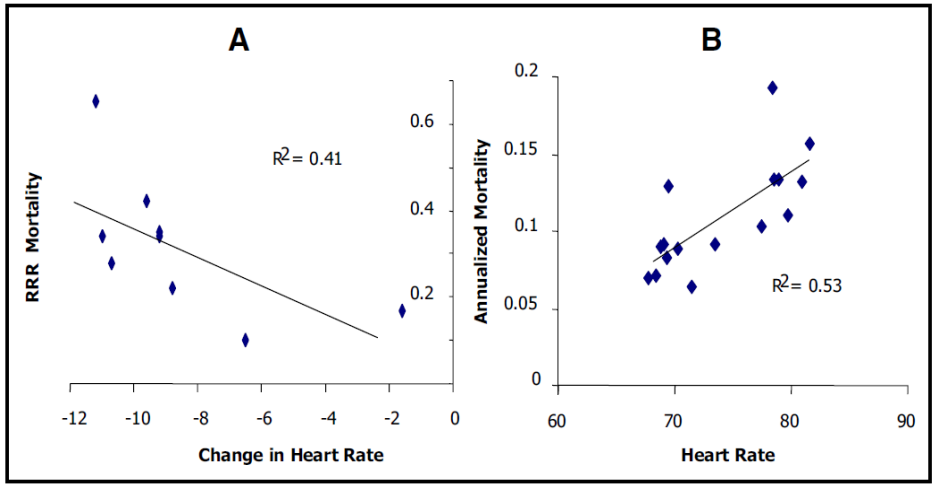
- Randomized Controlled Trials:
- HR Change vs. all-cause mortality, LVEF
- 35Trials (22,926 Pts), Mean FU 9.6 mon.
- Close relation,
  HR and all-cause annualized mortality
  (adjusted R^2=0.51, p=0.004)
- Strong correlation,
  Change in HR and change in LVEF
  (adjusted R^2=0.48, p=0.000)
  (R^2=0.60, p=0.0004 trials with >100pts)

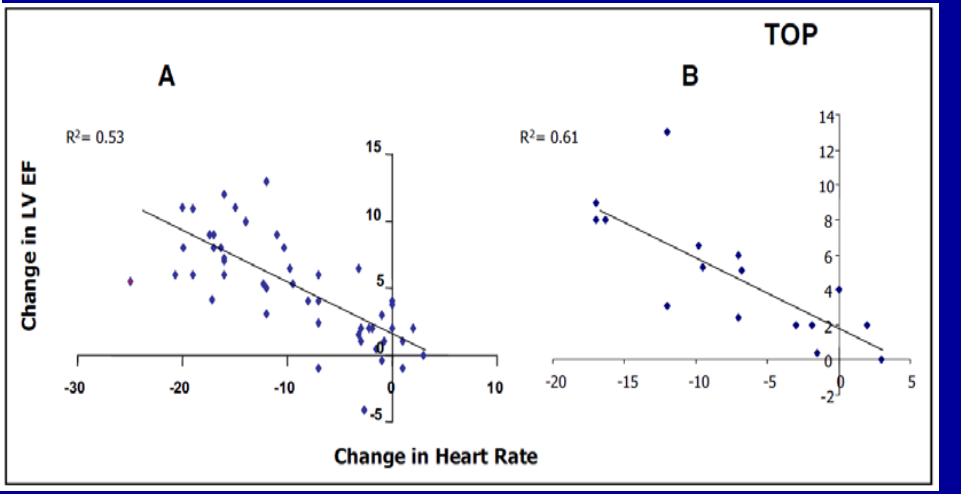
– Glannery G, et al Am J Cardiol 2008;101:865-869

HR Reduction on Clinical Outcome

Characteristics of controlled clinical trials: left ventricular ejection fraction versus mortality

Study	Comparator	β Blocker	No. Randomized (Arm 1/Arm 2)	Duration of Blinded Therapy (mo)	Baseline LVEF (%)	NYHA Class	Primary End Point
BEST[5]	Placebo	Bucindolol	1,354/1,354	24	≤35	III–IV	All-cause mortality
CIBIS[6]	Placebo	Bisoprolol	320/321	21	≤40	III–IV	Mortality
CIBIS II[7,8]	Placebo	Bisoprolol	1,320/1,327	15.6	≤35	III–IV	All-cause mortality
CIBIS III[9]	Enalapril	Bisoprolol	505/505	15	≤35	II–III	All-cause mortality or hospitalization
COMET[10]	Carvedilol	Metoprolol	1,511/1,518	58	<35	II–IV	All-cause mortality
COPERNICUS[11]	Placebo	Carvedilol	1,133/1,156	10.4	<25	III–IV	All-cause mortality
MERIT-HF[12]	Placebo	Metoprolol succinate	1,990/2,001	12	≤40	II–IV	All-cause mortality
SENIORS[13]	Placebo	Nebivolol	1,061/1,067	21	≤35 (65%); >35 (35%)	I–IV	All-cause mortality or CV hospital admission
US Carvedilol Heart Failure Study[14]	Placebo	Carvedilol	398/696	6	≤35	II–IV	Death or hospitalization due to CV cause





Dosage and HR-Reduction on Death

- Meta-analysis:
- Data source: MEDLINE, EMBASE, CINAHL, etc
- 23 Beta-Blocker trial, LVEF 17-36%
- >95% of 19202 Pts had systolic dysfunction

- Finlay A, et al Ann Inter Med. 2009;150:784-794

Dosage and HR-Reduction on Death

- Overall risk ratio for death 0.76(0.68-0.84)
- Moderate heterogeneity in magnitude of HRR
- No significant relationship between
  all cause mortality and BB-dosing
- Survival benefit of b-blocker
  Significantly ac magnitude of HR-Reduction
  Not significant with B-Blocker Dose

- Finlay A, et al Ann Inter Med. 2009;150:784-794

Dosage and HR–Reduction on Death

Table 1. **Baseline Data for Included Trials**

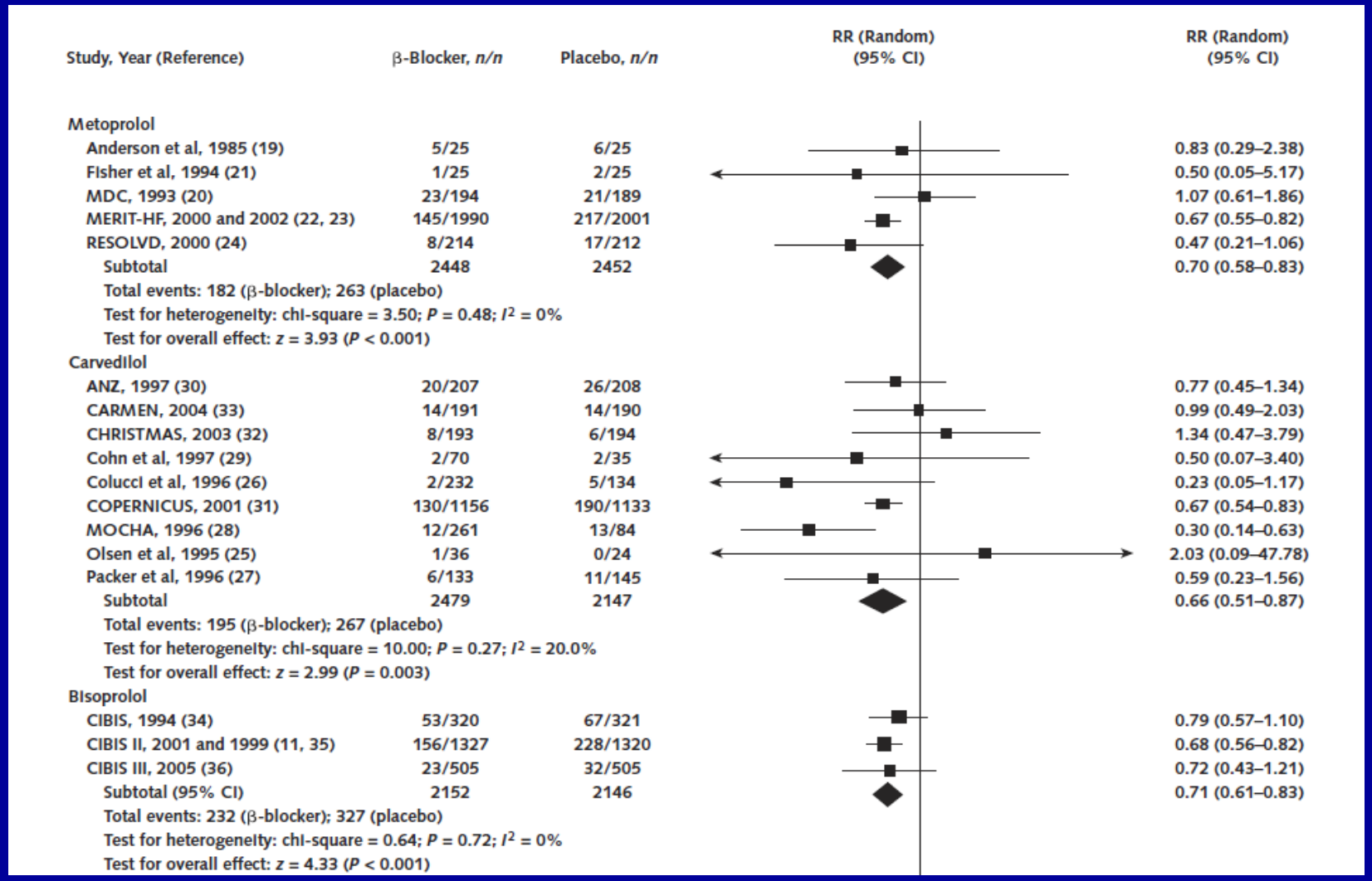
Study, Year (Reference)	Sample Size, *n*	Mean Age, *y*	Men, %	Inclusion Criteria
Metoprolol				
Anderson et al, 1985 (19)	50	51	66	LVEF <0.40, idiopathic dilated cardiomyopathy, no coronary disease
MDC, 1993 (20)*	383	49	72	Age 16–75 y, LVEF <0.40, idiopathic dilated cardiomyopathy, no coronary disease, HR >45 beats/min, SBP >90 mm Hg
Fisher et al, 1994 (21)	50	63	96	NYHA class II–IV, LVEF ≤0.40 with coronary disease, stable for 1 mo, HR >60 beats/min
MERIT-HF, 2000 (22) and 2002 (23) (high dose)	3047	63	77	Age 40–80 y, NYHA class II–IV, LVEF ≤0.40, HR >68 beats/min, SBP >100 mm Hg
MERIT-HF, 2000 (22) and 2002 (23) (low dose)	2449	64	78	Age 40–80 y, NYHA class II–IV, LVEF ≤0.40, HR >68 beats/min, SBP >100 mm Hg
RESOLVD, 2000 (24)	426	62	82	NYHA class II–IV, LVEF <0.40, 6-min walk test <500 m
Carvedilol				
Olsen et al, 1995 (25)	60	52	93	Age 18–80 y, NYHA class II–III, LVEF ≤0.35
Colucci et al, 1996 (26)	366	54	85	Age 18–85 y, NYHA class II–IV, LVEF ≤0.35, stable for 1 mo, SBP >85 mm Hg, 6-min walk test 425–550 m
Packer et al, 1996 (27)	278	60	73	NYHA class II–IV, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–450 m
MOCHA, 1996 (28) (low dose)	167	59	75	Age 18–85 y, NYHA class II–III, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–425 m
MOCHA, 1996 (28) (medium dose)	173	60	76	Age 18–85 y, NYHA class II–III, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–425 m
MOCHA, 1996 (28) (high dose)	173	60	77	Age 18–85 y, NYHA class II–III, LVEF ≤0.35, stable for 1 mo, HR >68 beats/min, SBP >85 mm Hg, 6-min walk test 150–425 m
Cohn et al, 1997 (29)	105	61	58	NYHA class III–IV, LVEF ≤0.35, SBP >85 mm Hg, 6-min walk test <450 m
ANZ, 1997 (30)	415	67	80	NYHA class II–IV, LVEF <0.45, ischemic heart disease, HR >50 beats/min, SBP >90 mm Hg
COPERNICUS, 2001 (31)	2289	63	80	NYHA class III–IV, LVEF <0.25, HR >68 beats/min, SBP >85 mm Hg
CHRISTMAS, 2003 (32)	387	63	90	NYHA class I–III, ischemic etiology, stable ≥2 wk, HR >60 beats/min, SBP >85 mm Hg, no specific LVEF criteria beyond "systolic dysfunction"
CARMEN, 2004 (33)	381	62	81	NYHA class I–III, LVEF <0.40, stable for 2 wk, if "no contraindications to β-blocker"

Dosage and HR–Reduction on Death

Bisoprolol				
CIBIS, 1994 (34)	641	60	83	NYHA class III–IV, LVEF <0.40, stable for 6 wk, HR >65 beats/min, SBP <160 mm Hg
CIBIS II, 1999 (35) and 2001 (11)	2647	61	80	NYHA class III–IV, LVEF ≤0.35, stable for 6 wk, HR >60 beats/min, SBP >100 mm Hg
CIBIS III, 2005 (36)†	1010	72	68	NYHA class II–III, age >65 y, LVEF ≤0.35, stable for 1 wk, HR >60 beats/min, SBP >100 mm Hg
Bucindolol				
Woodley et al, 1991 (37)	50	52	72	NYHA class II–III, LVEF ≤0.40, stable for 3 wk, HR >50 beats/min, SBP >80 mm Hg, without symptomatic AV block
Bristow et al, 1994 (38) (low dose)	72	53	64	NYHA class I–IV, LVEF
Bristow et al, 1994 (38) (moderate dose)	66	54	58	NYHA class I–IV, LVEF
Bristow et al, 1994 (38) (high dose)	69	54	59	NYHA class I–IV, LVEF
BEST, 2001 (39)	2708	60	78	NYHA class III–IV, LVEF ≤0.35, stable for 4 wk, HR >50 beats/min, SBP >80 mm Hg
Atenolol				
Sturm et al, 2000 (40)	100	52	88	NYHA class II–III, LVEF
Nebivolol				
SENIORS, 2005 (41)	2128	76	63	Age ≥70 y, NYHA class I–IV, hospitalization or LVEF ≤0.35, stable for 6 wk, HR >60 beats/min, SBP >90 mm Hg
ENECA, 2005 (42)	260	72	73	Age ≥65 y, NYHA class II–IV, LVEF ≤0.35, stable for 2 wk, HR >50 beats/min

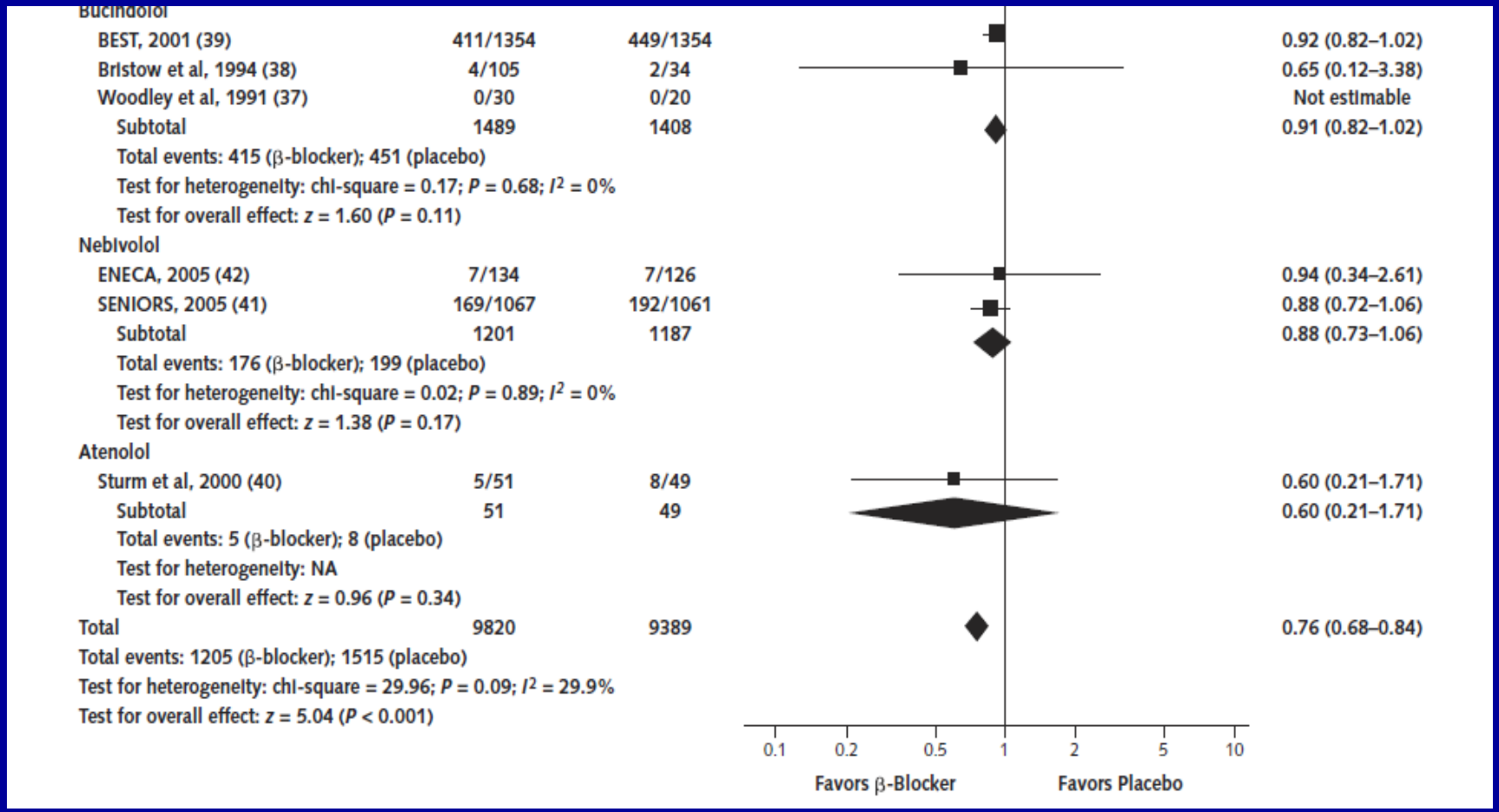
Dosage and HR-Reduction on Death

All-cause mortality in trials of 50 or more Pts. by agent



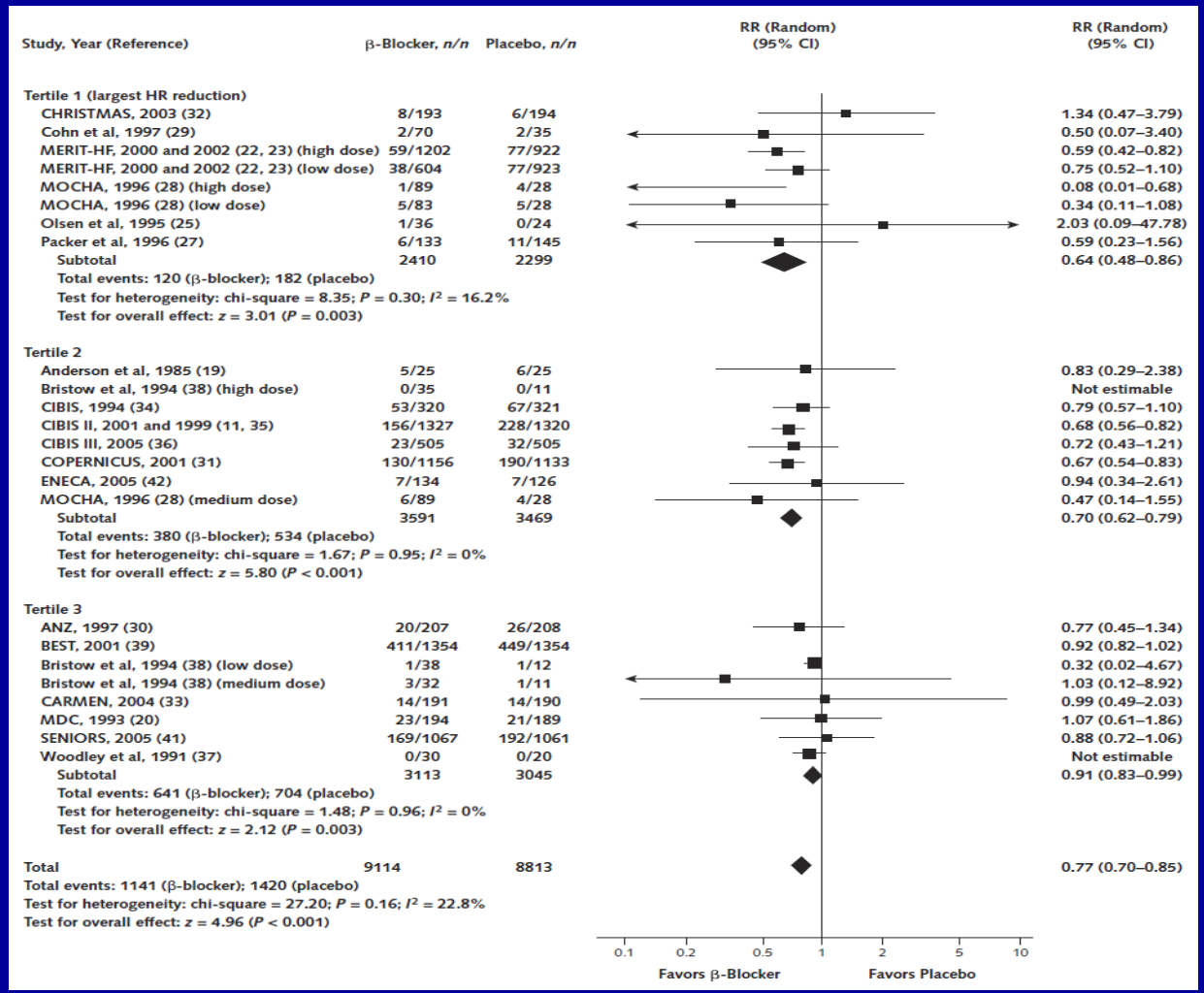
Dosage and HR-Reduction on Death

All-cause mortality in trials of 50 or more Pts. by agent

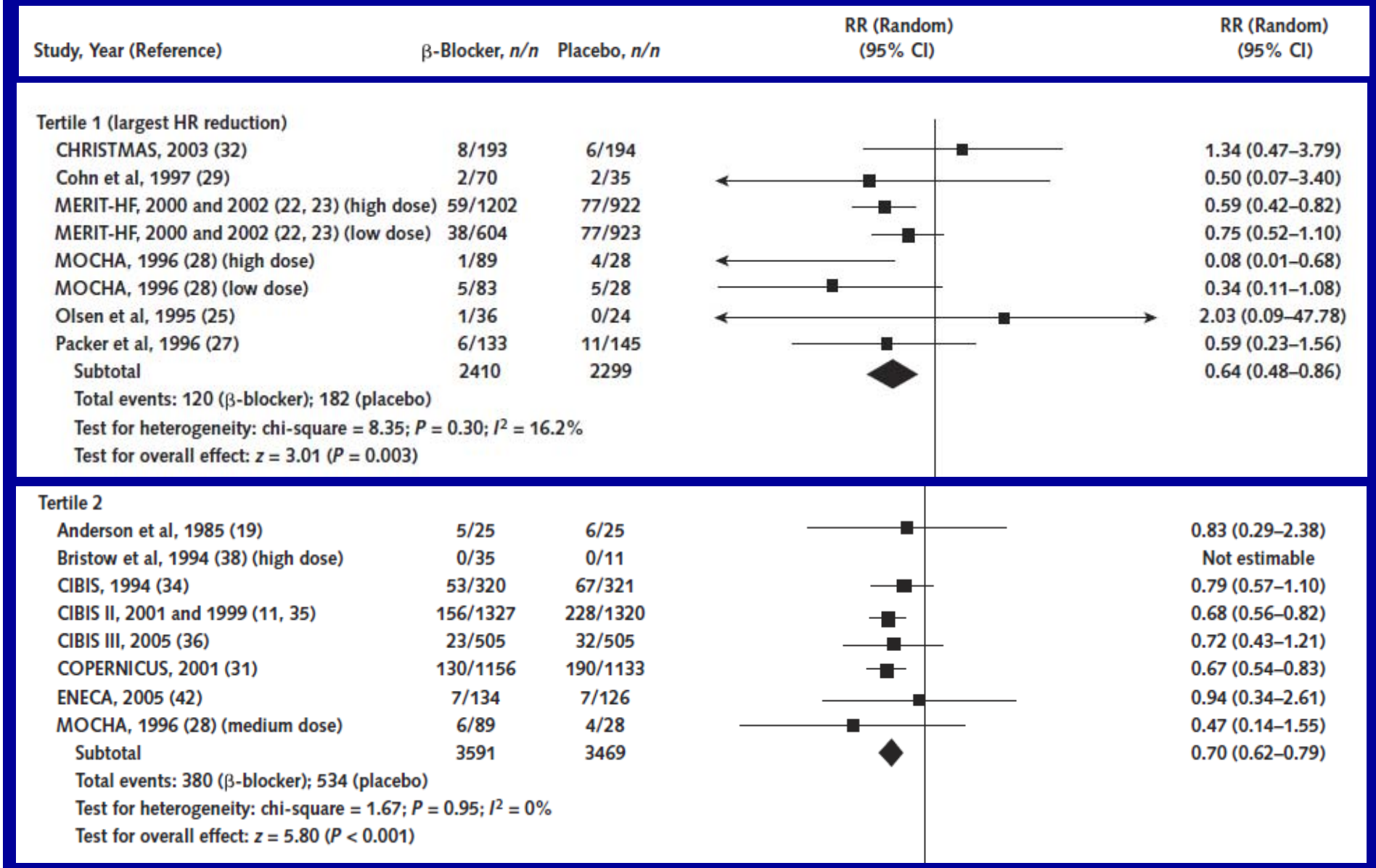


Dosage and HR-Reduction on Death

All-cause mortality, by Tx-related HR reduction tertile

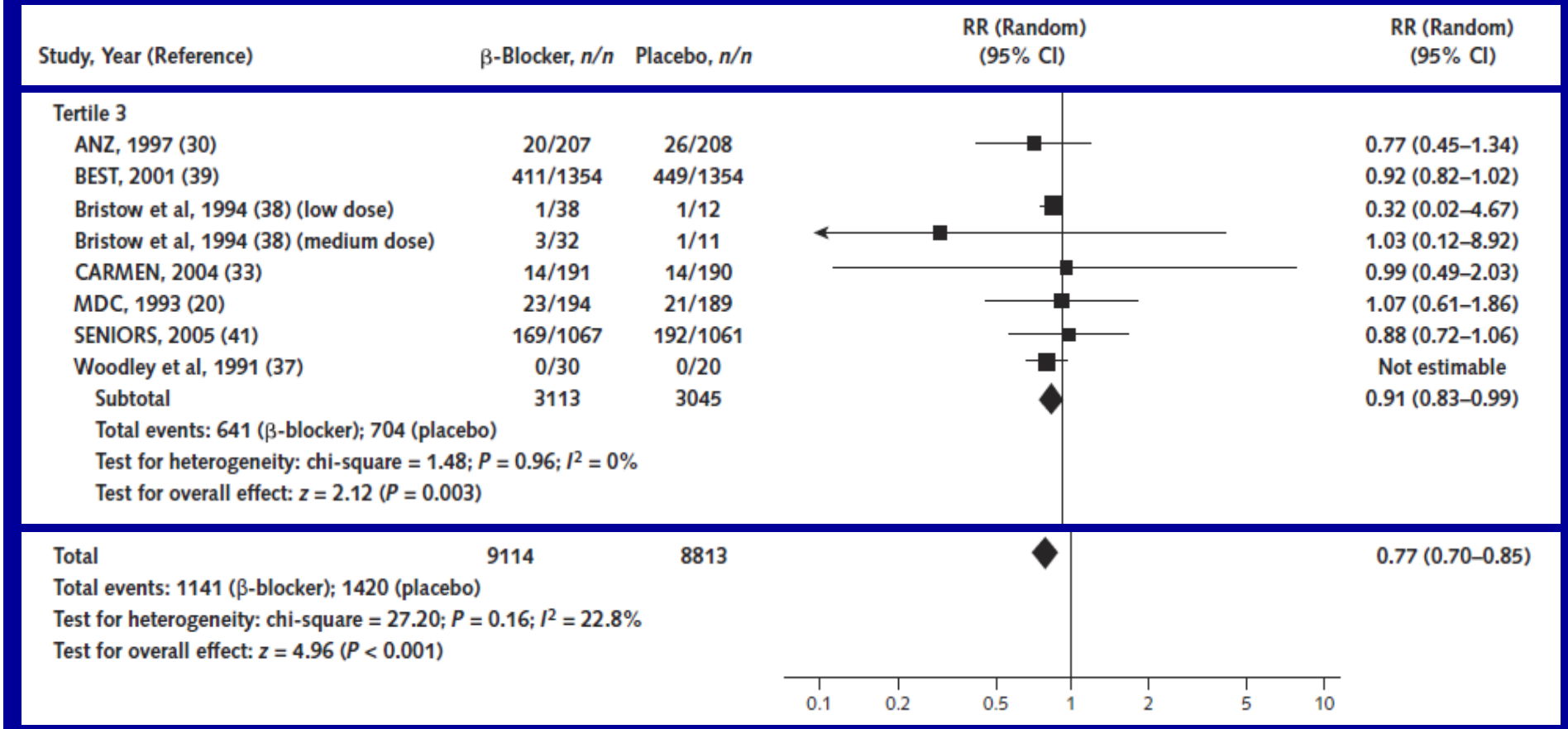


Dosage and HR-Reduction on Death



Study, Year (Reference)	β-Blocker, *n/n*	Placebo, *n/n*	RR (Random) (95% CI)	RR (Random) (95% CI)
Tertile 1 (largest HR reduction)				
CHRISTMAS, 2003 (32)	8/193	6/194		1.34 (0.47–3.79)
Cohn et al, 1997 (29)	2/70	2/35		0.50 (0.07–3.40)
MERIT-HF, 2000 and 2002 (22, 23) (high dose)	59/1202	77/922		0.59 (0.42–0.82)
MERIT-HF, 2000 and 2002 (22, 23) (low dose)	38/604	77/923		0.75 (0.52–1.10)
MOCHA, 1996 (28) (high dose)	1/89	4/28		0.08 (0.01–0.68)
MOCHA, 1996 (28) (low dose)	5/83	5/28		0.34 (0.11–1.08)
Olsen et al, 1995 (25)	1/36	0/24		2.03 (0.09–47.78)
Packer et al, 1996 (27)	6/133	11/145		0.59 (0.23–1.56)
Subtotal	2410	2299		0.64 (0.48–0.86)
Total events: 120 (β-blocker); 182 (placebo)				
Test for heterogeneity: chi-square = 8.35; $P = 0.30$; $I^2 = 16.2\%$				
Test for overall effect: $z = 3.01$ ($P = 0.003$)				
Tertile 2				
Anderson et al, 1985 (19)	5/25	6/25		0.83 (0.29–2.38)
Bristow et al, 1994 (38) (high dose)	0/35	0/11		Not estimable
CIBIS, 1994 (34)	53/320	67/321		0.79 (0.57–1.10)
CIBIS II, 2001 and 1999 (11, 35)	156/1327	228/1320		0.68 (0.56–0.82)
CIBIS III, 2005 (36)	23/505	32/505		0.72 (0.43–1.21)
COPERNICUS, 2001 (31)	130/1156	190/1133		0.67 (0.54–0.83)
ENECA, 2005 (42)	7/134	7/126		0.94 (0.34–2.61)
MOCHA, 1996 (28) (medium dose)	6/89	4/28		0.47 (0.14–1.55)
Subtotal	3591	3469		0.70 (0.62–0.79)
Total events: 380 (β-blocker); 534 (placebo)				
Test for heterogeneity: chi-square = 1.67; $P = 0.95$; $I^2 = 0\%$				
Test for overall effect: $z = 5.80$ ($P < 0.001$)				

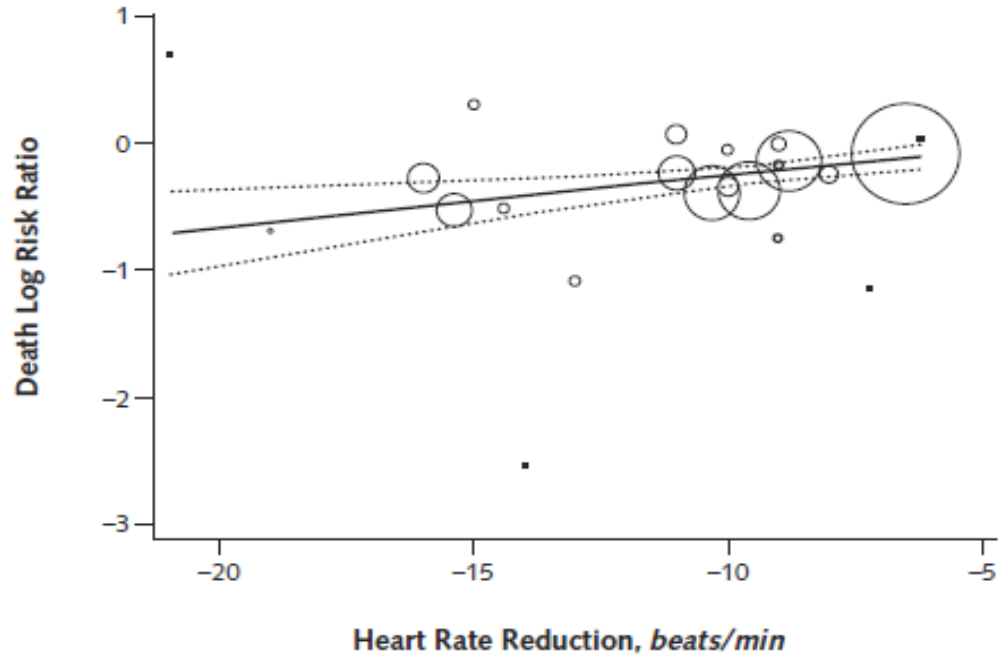
Dosage and HR-Reduction on Death



Dosage and HR-Reduction on Death

Magnitude of R reduction and risk ratio of all-cause mortality

Figure 4. **Meta-regression line for magnitude of heart rate reduction and risk ratio of all-cause mortality.**



Ivabradine vs. Metorpolol for HR Reduction

- 120 Pts, before coronary CT
- Ivabradine 15 mg or metoprolol 50 mg, PO
- Results:

  HR Reduction: −11.83 vs −13.20 bpm, p=NS

  (−13.19 vs. −10.04, p<0.05 in long-term BB user)

  DBP: −5.05 vs. −4.08 mmHg, p=NS

  SBP: −3.95 vs. −13.65 mmHg, p<0.001
- Ivabradine decreases HR sufficienty without significant SBP depression

  – Pichler P, et al. Am J Cardiol. 2012;109:169-73

In Summary,

- Up-titration of Beta-blocker is important
- To up-titrate the beta-blocker,
  Target HR is more important than target Dose
  Despite of T-dose, if HR do not reach T-HR?
- We must clarify the definition of:
  Target dose,
  Target Heart (absolute and change)

In Conclusion

- HR, very important simple biomarker
- Some extent may be Risk Marker

  above that level, may be change to Risk Factor
- In this situation modulation of HR is very important to improve the survival of HF
- Ivabradine, selective cardiac pacemaker I_f current inhibitor, may be used in this situation
- But, target HR-based appropriate use of beta-blocker is mandatory.

경청해 주셔서 감사합니다.