Web appendix

Table A. Characteristics of included studies

Trial	Inclusion	Exclusion	Enrollment Period	NYHA Class	ACEI	Target Dose	Mean Dose Achieved
ANZ	Ischemic HF, LVEF<45%	NYHA IV, HR<50,Heart Block	NA	II,III	86%	25 mg BID	41mg/d
BEST	Dilated CMP, LVEF<35%	HR<50,angina, valve disease	May 31, 1995-December 31, 1998	III,IV	91%	100 mg BID	76mg BID
Bristow	HF>1month,LVEF<40%	HR<50,Heart Block	NA	I,II,III,IV	87%	12.5 mg/d, 50mg/d, 200 mg/d	12.5mg, 44mg, 196 mg
CARMEN	HF>2month,LVEF<40%	recent or planned revascularisation	NA	I,II,III	70%	50 mg BID	47.9mg BID
Carvedilol Efficacy/Cohn	HF>3 months, LVEF<35%	Valvular disease, Heart Block	July 1993-March 1995	III,IV	94%	25 mg BID	23 mg BID
CHRISTMAS	HF Rx>2 weeks,LVEF<40%	HR<60, Age<40 years	April 1997-January 2001	I,II,III	87%	25 mg BID	25 mg BID

CIBIS	NYHA III/IV, LVEF<40%	Valvular disease, HR<65	March 1989-August 1992.	III,IV	89%	5 mg/d	3.8 mg/d
CIBIS II	NYHA III/IV, LVEF<35%	HR<60, Heart Block	NA	III,IV	96%	10 mg/d	8.6 mg/d
CIBIS III	>65 years, NYHA II/III, LVEF<35%	HR<60, Advanced Heart Block	NA	II,III	100%	10 mg/d	7.2 mg/d
Colucci	HF Rx>2 months,LVEF<35%	Valvular disease, Heart Block	NA	II,III	98%	25 mg BID	25 mg BID
COPERNICUS	HF>2 months,LVEF<25%	Valvular disease, HR<68	October 28, 1997-March 20, 2000	II	97%	25 mg BID	37 mg/d
ENECA	>65 years, NYHA II/III/IV, LVEF<35%	Valvular disease, HR<50	NA	II,III,IV	91%	10 mg/d	7.4 mg/d
MERIT HF 2000 and 2002	HF>3 months, LVEF<40%	Recent AMI, SBP<100 mm of Hg	February 14, 1997-October 31, 1998	II,III,IV	89%	200 mg/d	NA
MOCHA/Bristow	HF>3 months, LVEF<35%	Valvular disease, Heart Block	NA	II,III	99%	6.25 mg, 12.5 mg, 25 mg BID	6.25mg, 12.3mg, 23.7mg BID
Packer	HF>3 months,	Valvular	April 29,	II,III,IV	95%	25 mg	47 mg/d

	LVEF<35%	disease, HR<68	1993-February 3, 1995			BID	
PRECISE	HF>3 months, LVEF<35%	Valvular disease, HR<68, Heart Block	NA	II,III,IV	96%	25 mg BID	28 mg/d
RESOLVD	NYHA II-IV, LVEF<40%	NA	NA	I,II,III,IV	14%	200 mg/d	156 mg/d
SENIORS	>70 years, LVEF<35%	Valvular disease, HR<60	NA	II,III,IV	81.70%	10 mg/d	7.7 mg/d
Sturm	18-75 years, LVEF<25%	Recent ADHF in 6 weeks	April 1996-November 1998	II,III,IV	100%	100 mg/d	89 mg/d
Waagstein-MDC	16-75 years, LVEF<40%	SBP<90 mm of Hg, HR<45	September, 1986-July, 1991	I,II,III,IV	78%	150 mg/d	108 mg/d
COMET	NYHA II-IV, LVEF<35%	Valvular heart disease, HR<60	NA	II,III,IV	92%	25 mg BID/50 mg BID	41.8 mg/d, 85 mg/d

HF=Heart failure
LVEF= Left ventricular ejection fraction
NYHA=New York Heart Association\
SBP=Systolic blood pressure
NA=Not available
AMI=Acute myocardial infarction
HR=Heart rate
ADHF=Acute decompensated heart failure

Table B. Risk of bias summary per Cochrane metrics. '+' indicates present

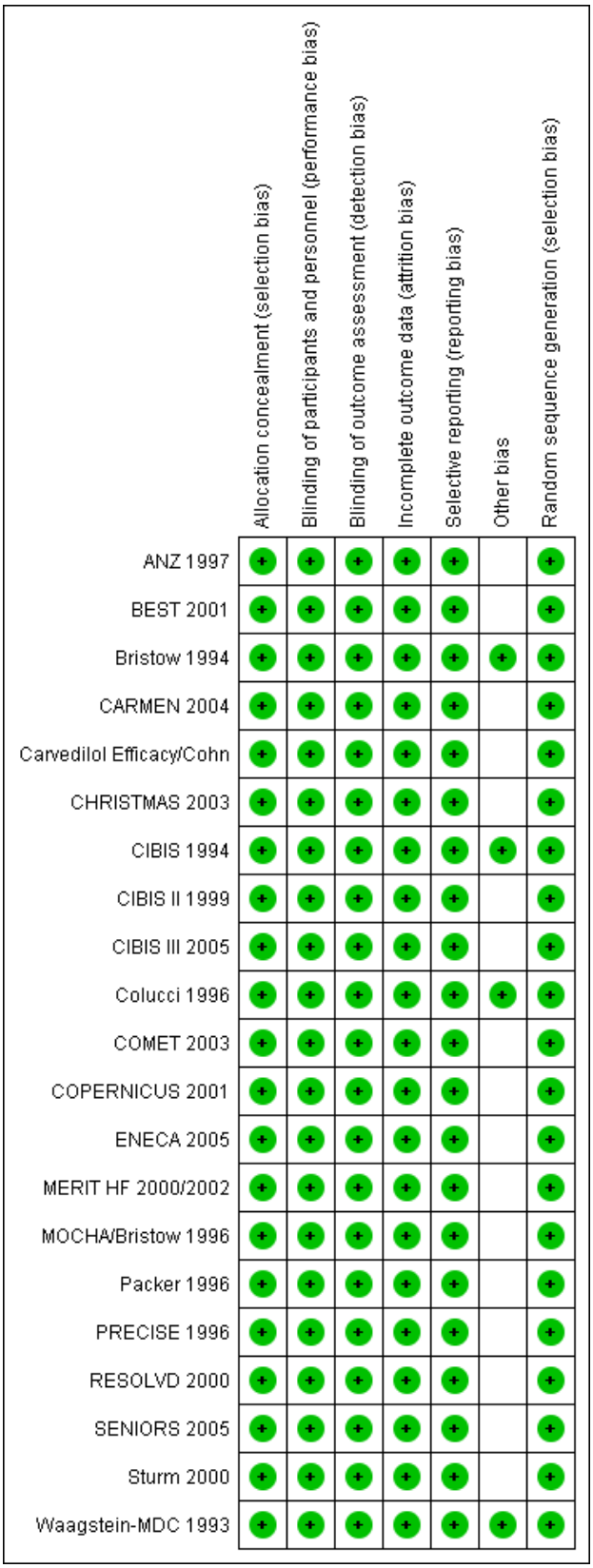

Table C. Hazard ratio analysis after a median follow-up of 12 months

Agent	Death (Primary Outcome) [21 studies]	Cardiovascular death (Secondary Outcome) [13 studies]	Sudden death (Secondary Outcome) [12 studies]	Drug discontinuation (Secondary Outcome) [21 studies]
Any beta-blocker	**HR=0.74 (0.63-0.84) vs placebo/standard Rx**	**HR=0.77 (0.57-0.93) vs placebo/standard Rx**	**HR=0.74 (0.56-0.92) vs placebo/standard Rx**	HR=0.92 (0.80-1.01) vs placebo/standard Rx
Atenolol	HR=0.59 (0.16-2.06) vs placebo/standard Rx HR=0.85 (0.22-3.13) vs bisoprolol HR=0.65 (0.39-6.26) vs bucindolol HR=0.89 (0.23-3.23) vs carvedilol HR=0.83 (0.21-3.13) vs metoprolol HR=0.67 (0.16-2.56) vs nebivolol	HR=0.66 (0.13-3.47) vs placebo/standard Rx HR=0.92 (0.14-5.88) vs bisoprolol HR=0.79 (0.12-5.56) vs bucindolol HR=1.18 (0.21-7.14) vs carvedilol HR=0.51 (0.06-4.17) vs metoprolol HR=0.76 (0.11-5.00) vs nebivolol	HR=0.46 (0.06-2.62) vs placebo/standard Rx HR=0.69 (0.07-4.55) vs bisoprolol HR=0.53 (0.06-4.00) vs bucindolol HR=0.71 (0.10-5.55) vs carvedilol HR=0.30 (0.03-2.78) vs metoprolol HR=0.75 (0.08-6.25) vs nebivolol	HR=0.76 (0.37-1.50) vs placebo/standard Rx HR=0.81 (0.37-1.75) vs bisoprolol HR=0.59 (0.18-1.92) vs bucindolol HR=0.86 (0.41-1.82) vs carvedilol HR=0.89 (0.41-1.89) vs metoprolol HR=0.74 (0.34-1.67) vs nebivolol
Bisoprolol	HR=0.69 (0.46-1.03) vs placebo/standard Rx HR=0.77 (0.40-1.52) vs bucindolol HR=1.03 (0.67-1.72) vs carvedilol HR=0.98 (0.54-1.72) vs metoprolol HR=0.78 (0.40-1.47) vs nebivolol	HR=0.72 (0.29-1.76) vs placebo/standard Rx HR=0.85 (0.22-3.33) vs bucindolol HR=1.27 (0.44-4.17) vs carvedilol HR=0.55 (0.11-2.70) vs metoprolol HR=0.83 (0.22-3.03) vs nebivolol	HR=0.66 (0.29-1.72) vs placebo/standard Rx HR=0.76 (0.22-3.13) vs bucindolol HR=0.99 (0.43-4.17) vs carvedilol HR=2.30 (0.43-10.82) vs metoprolol HR=1.08 (0.25-5.26) vs nebivolol	HR=0.94 (0.67-1.26) vs placebo/standard Rx HR=0.72 (0.25-1.96) vs bucindolol HR=1.06 (0.76-1.56) vs carvedilol HR=1.11 (0.68-1.68) vs metoprolol HR=0.92 (0.57-1.56) vs nebivolol
Bucindolol	HR=0.90 (0.52-1.51) vs placebo/standard Rx HR=1.33 (0.76-2.50) vs carvedilol HR=1.28 (0.63-2.44) vs metoprolol HR=1.03 (0.48-2.08) vs nebivolol	HR=0.85 (0.30-2.26) vs placebo/standard Rx HR=1.47 (0.47-5.26) vs carvedilol HR=0.65 (0.12-3.33) vs metoprolol HR=0.98 (0.24-3.70) vs nebivolol	HR=0.88 (0.32-2.29) vs placebo/standard Rx HR=1.28 (0.49-5.26) vs carvedilol HR=0.56 (0.11-2.94) vs metoprolol HR=1.41 (0.15-3.52) vs nebivolol	HR=1.29 (0.51-3.56) vs placebo/standard Rx HR=1.49 (0.57-4.17) vs carvedilol HR=1.52 (0.57-4.35) vs metoprolol HR=1.28 (0.47-3.85) vs nebivolol
Carvedilol	**HR=0.67 (0.48-0.85) vs placebo/standard Rx** HR=0.95 (0.55-1.49) vs metoprolol	HR=0.57 (0.28-1.01) vs placebo/standard Rx HR=0.43 (0.09-1.72) vs metoprolol	HR=0.66 (0.27-1.06) vs placebo/standard Rx HR=0.43 (0.08-1.61) vs metoprolol	HR=0.88 (0.68-1.05) vs placebo/standard Rx HR=1.04 (0.67-1.45) vs metoprolol

	HR=0.77 (0.40-1.28) vs nebivolol	HR=0.66 (0.19-1.87) vs nebivolol	HR=1.08 (0.21-1.08) vs nebivolol	HR=0.85 (0.56-1.35) vs nebivolol
Metoprolol	HR=0.71 (0.47-1.07) vs placebo/standard Rx HR=0.80 (0.42-1.54) vs nebivolol	HR=1.31 (0.35-4.90) vs placebo/standard Rx HR=1.52 (0.29-7.69) vs nebivolol	HR=1.54 (0.39-5.71) vs placebo/standard Rx HR=2.50 (0.39-14.29) vs nebivolol	HR=0.85 (0.62-1.18) vs placebo/standard Rx HR=0.83 (0.53-1.45) vs nebivolol
Nebivolol	HR=0.88 (0.54-1.48) vs placebo/standard Rx	HR=0.87 (0.34-2.27) vs placebo/standard Rx	HR=0.61 (0.18-2.04) vs placebo/standard Rx	HR=1.03 (0.66-1.44) vs placebo/standard Rx

Table D. Absolute risk reductions (ARR), percentages and number needed to treat (NNT) for individual beta blockers

Beta-Blocker	ARR(%)	HCI ARR	LCI ARR	NNT	HCI NNT	LCI NNT
Atenolol	6.50%	19.70%	–6.65%	15	–15	5
Bisoprolol	4.50%	6.46%	2.45%	22	41	15
Bucindolol	4.05%	13.46%	7.43%	25	149	13
Carvedilol	6.60%	8.20%	4.90%	15	20	12
Metoprolol	3.30%	4.89%	1.66%	31	60	20
Nevibolol	2.11%	5.03%	–0.80%	47	-123	19

HCI= Higher 95% Confidence Interval
LCI= Lower 95% Confidence Interval

Figure A. Meta-analysis of trials with <12 months of follow-up

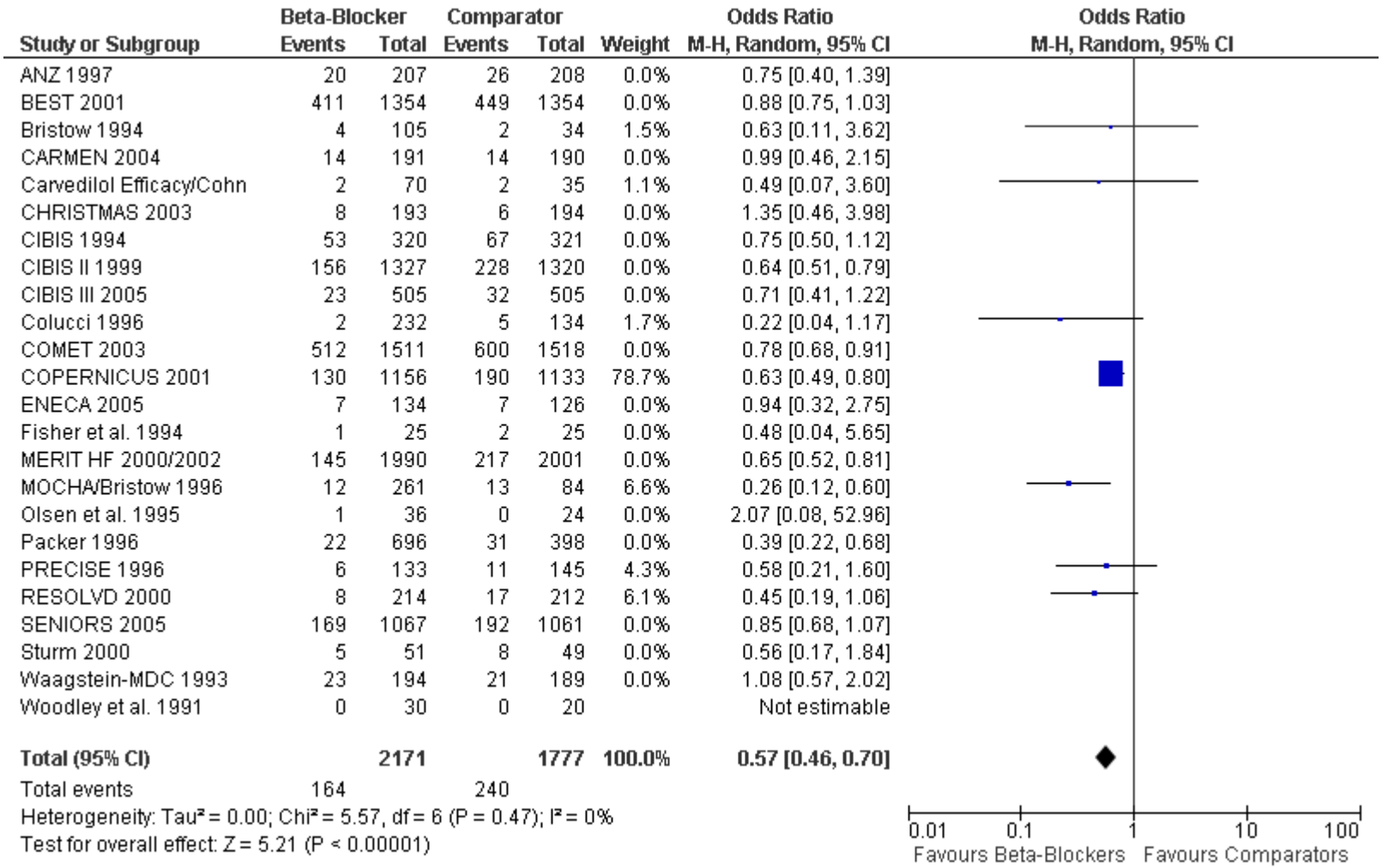

Figure B. Meta-analysis of trials with >12 months of follow-up

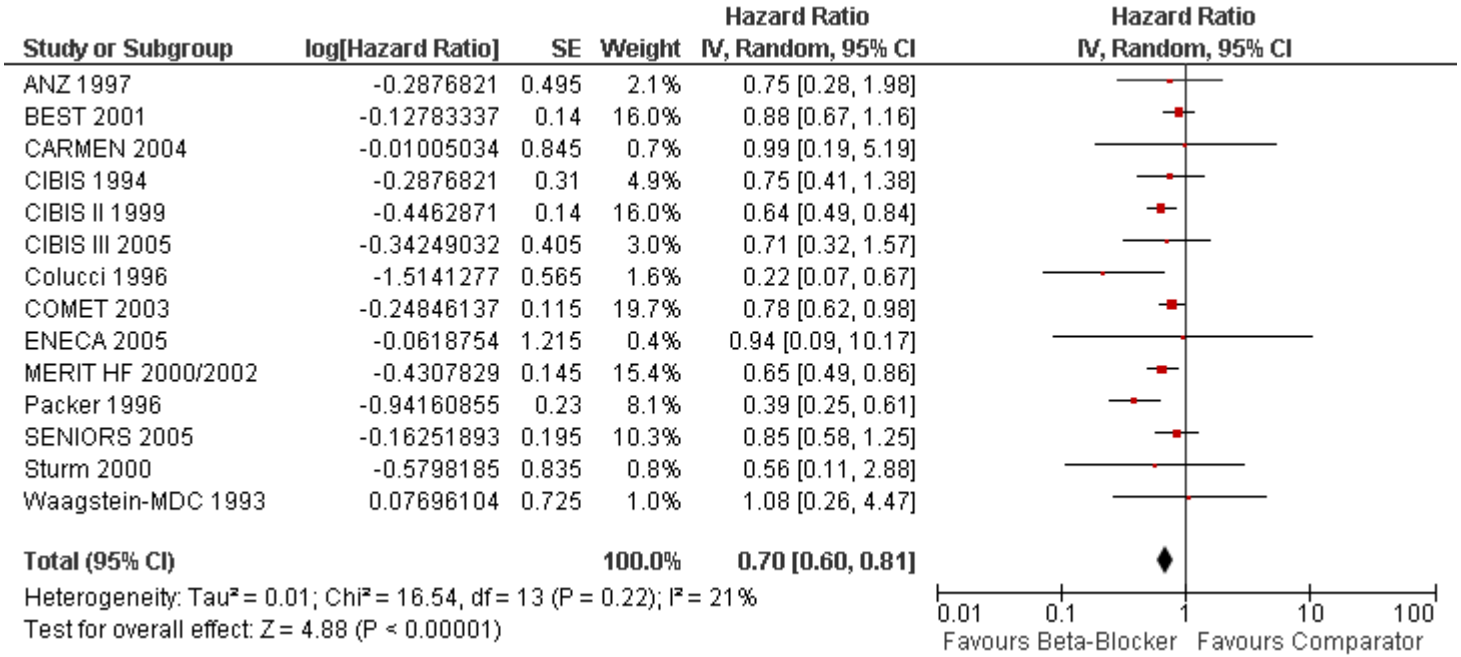

Figure C. Meta-analysis of trials conducted in US

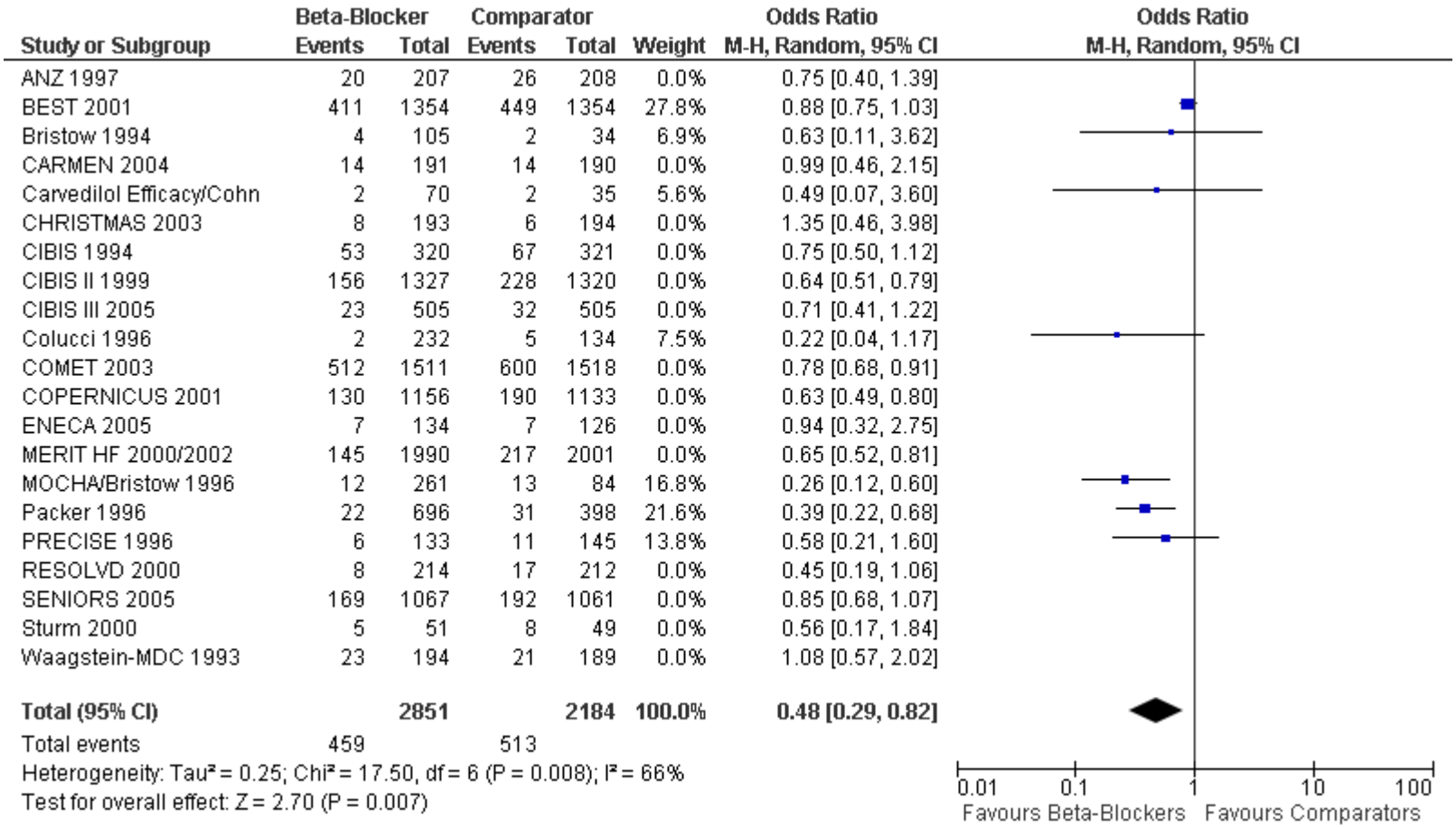

Figure D. Meta-analysis of trials with sample size 50 (instead of 100)