Bye Bye β-blockade?

β-blockers in stable CAD

Andrea Cartwright

Doctor of Pharmacy student

University of British Columbia

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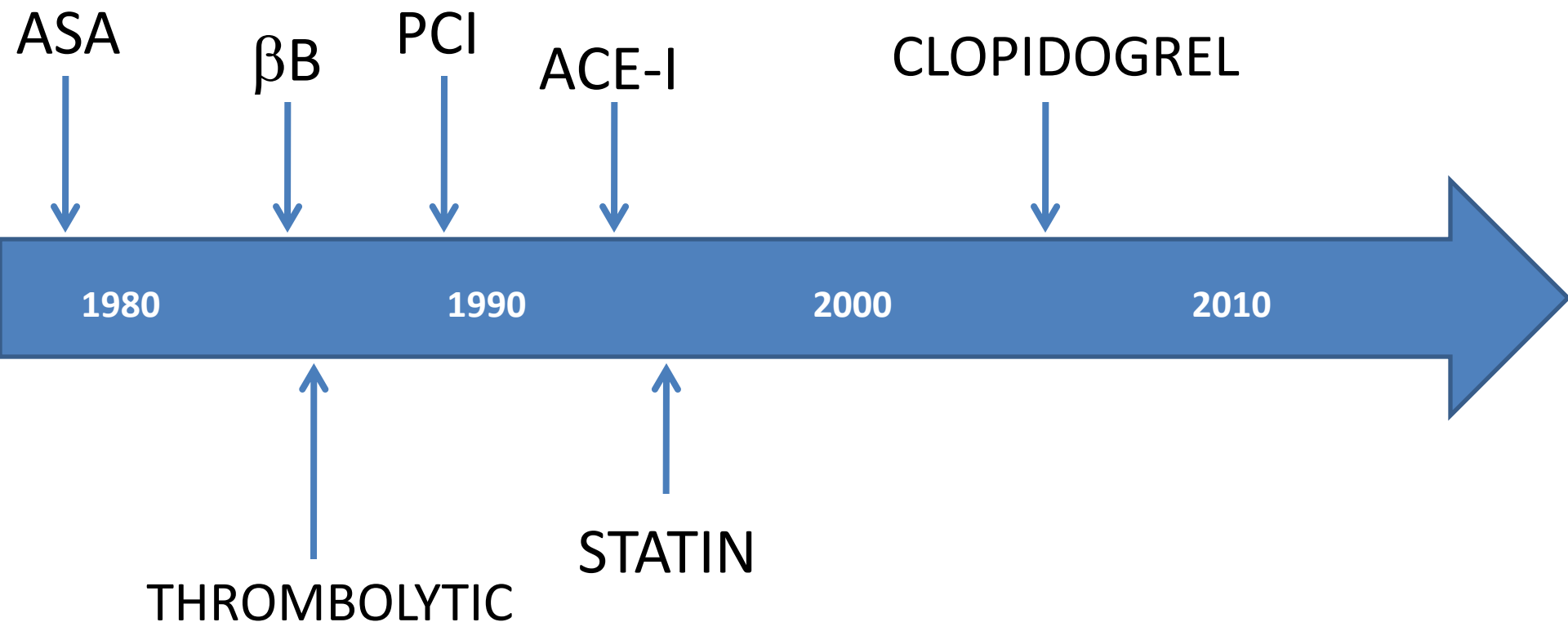
Acute Coronary Syndrome

Going back in time…



ACUTE CORONARY SYNDROME

- Rx = Statin, β-blocker, ACE-I, ASA, clopidogrel

β-blocker

↓myocardial O2 demand

↓infarct size

↓ transmural damage

ACUTE CORONARY SYNDROME

<u>β-blocker</u>

30d post ACS…

↓ re-infarction

↓ Ventricular fibrillation

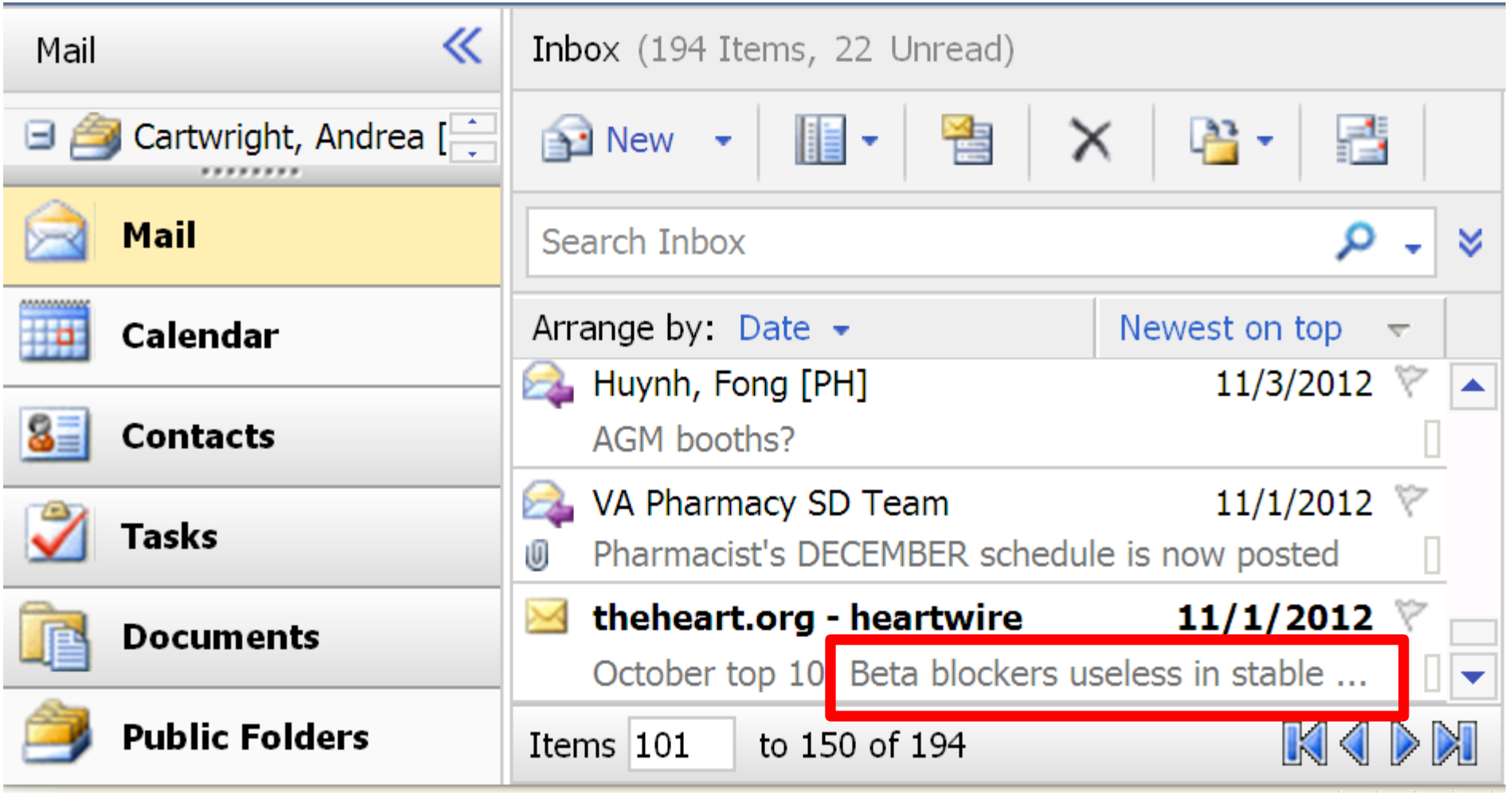
↔Mortality

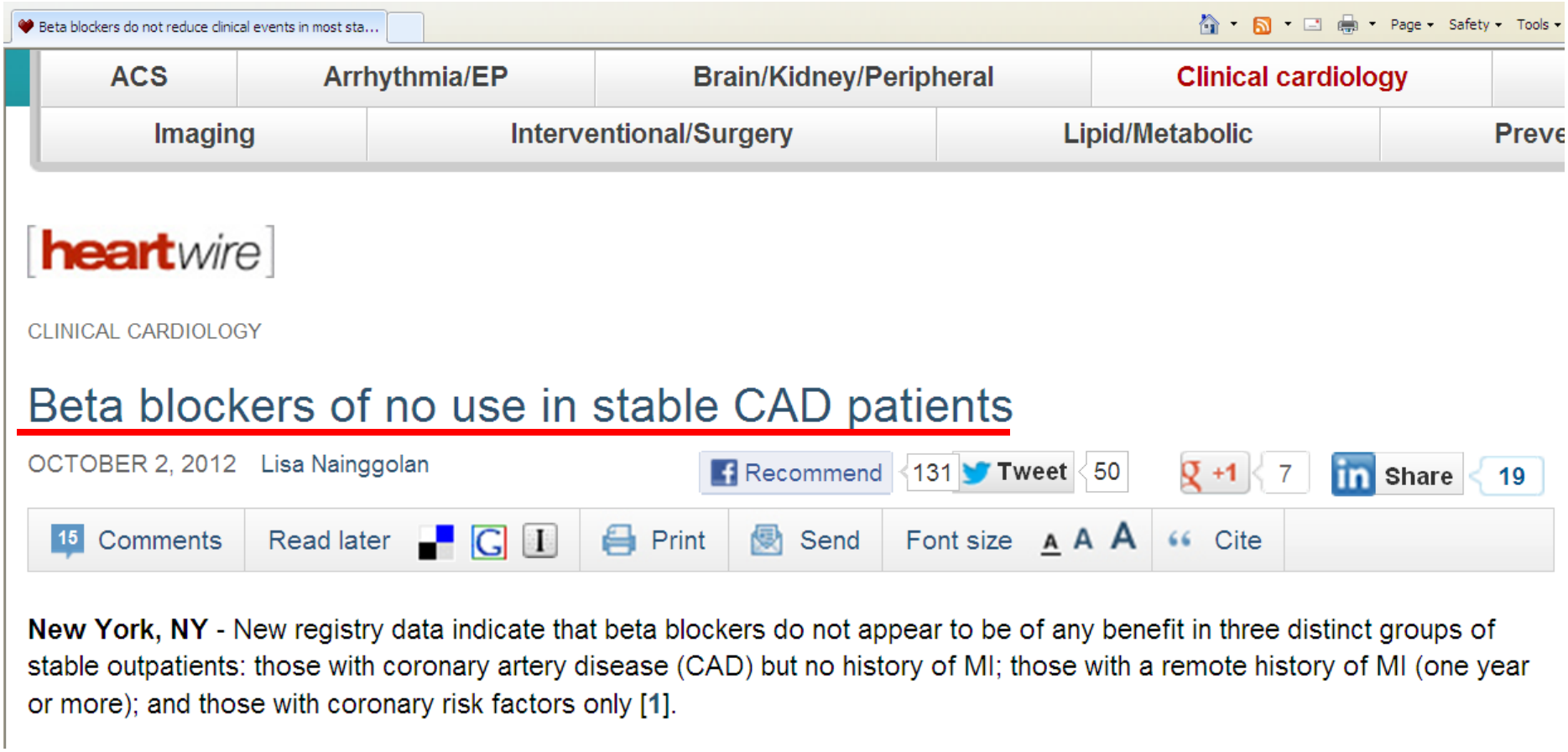
For how much longer will I need to take these drugs?

ACUTE CORONARY SYNDROME

- β-blocker duration
  - 2011 AHA/ACCF CVD 2° Prevention Guidelines
    - "started and continued for 3 years after MI or ACS" (Class I)
    - "reasonable to continue beyond 3 years" (Class IIa)
    - "considered for all others with coronary or vascular disease" (Class IIb)
  - 2011 ESC NSTEMI Guidelines
    - "recommended in all patient with reduced LVEF" (Class I)

October 2, 2012





The end of an era???

CLINICAL QUESTION

- In a patient with history of MI two years ago and normal LVEF, is indefinite treatment with a beta-blocker effective and safe?
  - Mortality?
  - Cardiovascular morbidity?
  - Adverse events?

β-Blocker Use and Clinical Outcomes in Stable Outpatients With and Without Coronary Artery Disease

Sripal Bangalore, MD, MHA
Ph. Gabriel Steg, MD
Prakash Deedwania, MD
Kevin Crowley, MS
Kim A. Eagle, MD
Shinya Goto, MD, PhD
E. Magnus Ohman, MD
Christopher P. Cannon, MD
Sidney C. Smith Jr, MD
Uwe Zeymer, MD
Elaine B. Hoffman, PhD
Franz H. Messerli, MD
Deepak L. Bhatt, MD, MPH
for the REACH Registry Investigators

JAMA. 2012;308(13):1340-1349

STUDY DESIGN

D	MC, prospective observational cohort, f/u 44 months, 2003-2009
P	N = 44 708, mean age 69, 40% N.American -14 043 prior MI: 75% male, 75% ASA, 75% statin, 70% ACE/ARB -12 012 CAD w/o MI: 66% male, 75% ASA, 71% statin, 70% ACE/ARB -18 653 CAD risk factors: 50% male, 57% ASA, 64% statin, 70% ACE/ARB
I	Beta-blocker use at time of enrolment
C	No beta-blocker use at time of enrolment
O	1°: CV death + nonfatal MI/stroke 2°: 1° + hosp for atherothrombotic events (ATE) or revasc 3°: all-cause death, CV death, nonfatal MI/stroke, hosp

RESULTS – Prior MI

OUTCOME	BB (n=3379)	No BB (n=3379)	RESULT
CV death, NF MI/stroke (%)	16.93	18.6	HR 0.9 [0.79-1.03]
CV death, NF MI/stroke, hosp for ATE/revasc (%)	30.96	33.12	OR 0.91 [0.82-1.00]
CV death (%)	9.68	10.27	p=0.31
MI (%)	5.5	5.51	P=0.28

***Similar results in propensity score-adjusted model**

RESULTS

- Sensitivity analysis
  - Excluding HF patients: similar results
  - Recent MI ($\leq$ 1y): $\downarrow$ secondary outcome, $\downarrow$ hospitalization, $\leftrightarrow$ primary outcome
  - HF cohort: $\leftrightarrow$ primary outcome

AUTHORS CONCLUSIONS

- β-blocker use not associated with lower event rate at 44 months among patients with history of MI (> 1 year prior)
- Further studies required to identify subgroups that may benefit and determine optimal duration of β-blocker use

STRENGTHS

- Propensity score matching
- ITT analysis
- Regression adjustment with propensity score to include all patients
- Tested for internal validity
  - statin analysis using same patient registry found significant benefit (HR 0.73)

LIMITATIONS

- Patients with data on BB enrolled from registry → bias?
- “Greedy” matching protocol → sub-optimal matching?
- Unmatched patients excluded
- Matched cohorts underpowered
- ITT based on BB use at time of enrolment
- No data on type of BB used, dosing, reason for non-use
- Observational design → potential for unmeasured confounders

WHY ARE WE USING BETA-BLOCKERS?!?

Search Strategy

Databases	Medline, EMBASE, Cochrane
Search Terms	Coronary artery disease, stable angina, coronary stenosis, coronary thrombosis, atherosclerosis, arteriosclerosis, adrenergic beta-antagonists, beta-blocker
Limits	English, Human, clinical trial or meta-analysis or systematic review, post-ACS, follow-up > 1 year
Results	-1 meta-analysis -1 RCT -1 retrospective cohort study -1 prospective cohort study

β Blockade after myocardial infarction: systematic review and meta regression analysis

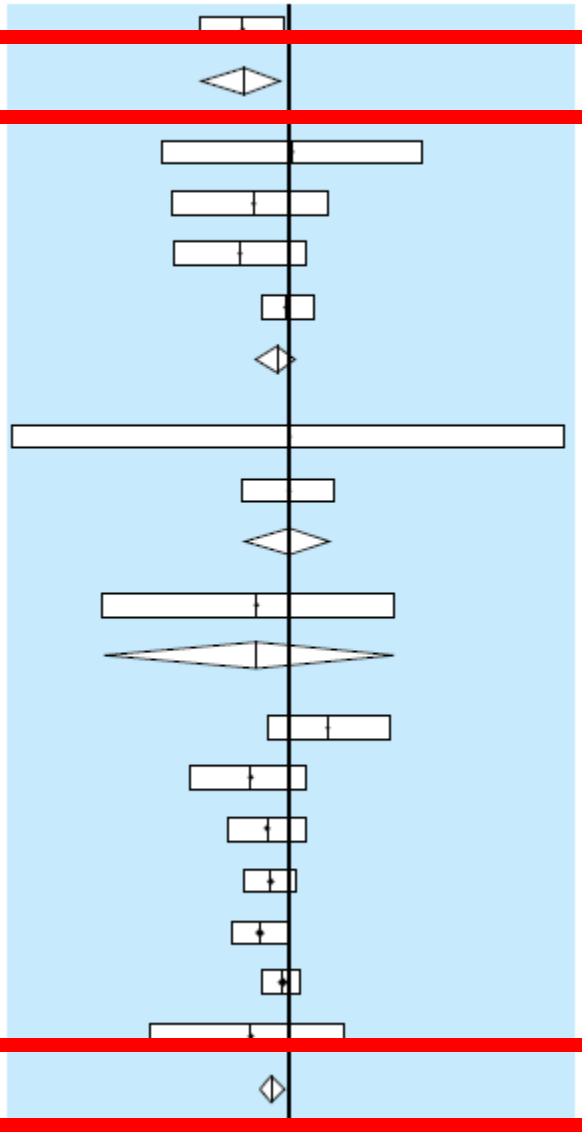
Nick Freemantle, John Cleland, Philip Young, James Mason, Jane Harrison

BMJ VOLUME 318 26 JUNE 1999

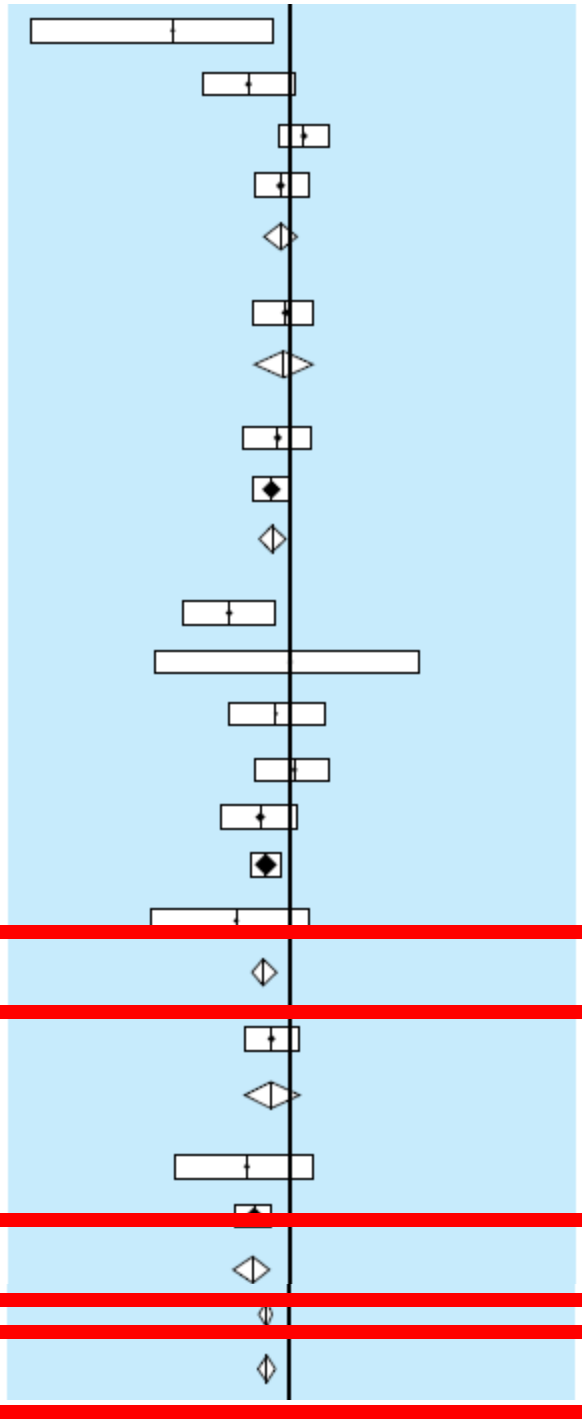
STUDY DESIGN

D	Systematic review, RCTs up to 1997
P	N = 24 974, acute or past MI 31 RCTs, median publication date 1982 Follow-up 6-48 mos (mean 18 mos)
I	Beta-blocker use
C	Placebo or no beta-blocker use
O	All-cause mortality, non-fatal reinfarction

RESULTS – Death



Trial	Weight (%)	Odds ratio (95% CI)
Boissel 1990[w51]	2.9	0.49 (0.25 to 0.93)
Acebutolol pooled	2.9	0.49 (0.25 to 0.93)
Reynolds 1972[w72]	0.3	1.03 (0.13 to 8.21)
Ahlmark 1974[w49]	0.8	0.58 (0.15 to 1.94)
Wilhelmsson 1974[w79]	1.2	0.48 (0.16 to 1.33)
Andersen 1979[w50]	4.3	0.96 (0.62 to 1.47)
Alprenolol pooled	6.6	0.83 (0.59 to 1.17)
Wilcox 1980a[w78]	0.1	1.02 (0.48 to 2.16)
Yusuf 1979[w80]	1.5	1.00 (0.01 to 86.25)
Atenolol pooled	1.6	1.02 (0.52 to 1.99)
Basu 1997[w56]	0.3	0.62 (0.05 to 5.61)
Carvedilol pooled	0.3	0.62 (0.05 to 5.61)
Rehnqvist 1980[w70]	0.7	0.56 (0.11 to 2.53)
López 1993[w75]	1.4	1.91 (0.76 to 5.05)
Manger Cats 1983[w65]	2.4	0.55 (0.21 to 1.36)
Rehnqvist 1984[w71]	4.6	0.73 (0.39 to 1.35)
Salathia 1985[w73]	5.4	0.76 (0.49 to 1.18)
LIT Research Group 1987[w64]	7.9	0.92 (0.67 to 1.27)
Hjalmarson 1981[w61]	0.5	0.62 (0.40 to 0.96)
Metoprolol pooled	23.1	0.80 (0.66 to 0.96)



European infarction study 1984[w58]	1.0	1.33 (0.87 to 2.04)
Schwartz 1992[w74] (high risk)	2.4	0.16 (0.02 to 0.79)
Schwartz 1992[w74] (low risk)	3.8	0.53 (0.26 to 1.06)
Taylor 1982[w76]	4.6	0.92 (0.61 to 1.41)
Oxprenolol pooled	11.8	0.91 (0.71 to 1.17)
Australian and Swedish study 1983[w53]	3.6	0.96 (0.60 to 1.55)
Pindolol pooled	3.6	0.96 (0.60 to 1.55)
Barber 1967[w55]	2.9	0.87 (0.51 to 1.50)
Multicentre international study 1975[w67]	11.0	0.78 (0.59 to 1.03)
Practolol pooled	13.9	0.80 (0.63 to 1.02)
Kaul 1988[w63]	2.4	1.00 (0.12 to 8.31)
Mazur 1984[w66]	0.2	0.44 (0.11 to 1.43)
Wilcox 1980a[w78]	1.5	0.86 (0.40 to 1.84)
Baber 1980[w54]	2.3	1.07 (0.59 to 1.93)
Aronow 1997[w52]	3.1	0.40 (0.19 to 0.83)
Hansteen 1982[w60]	16.0	0.65 (0.37 to 1.15)
BHAT Trial Research Group 1982[w57]	1.0	0.72 (0.56 to 0.91)
Propranolol pooled	26.6	0.71 (0.59 to 0.85)
Julian 1982[w62]	5.3	0.81 (0.54 to 1.21)
Sotalol pooled	5.3	0.81 (0.54 to 1.21)
Roqué 1987[w77]	1.0	0.53 (0.17 to 1.54)
Norwegian Multicentre Study Group 1981[w68]	12.6	0.60 (0.45 to 0.79)
Timolol pooled	13.6	0.59 (0.46 to 0.77)
Fixed effects pooled	100	0.77 (0.70 to 0.84)
Full random effects pooled	100	0.77 (0.69 to 0.85)

RESULTS

	OR [95% CI]	Annual reduction/100 pts	NNT/y
DEATH	**0.77** [0.69-0.85]	**-1.2** [0.6-1.7]	**84**

	Annual reduction/100 pts	NNT/y
RE-INFARCTION	**-0.9** [0.3-1.6]	**107**

***Pooled random effects (all trials)**

RESULTS – Withdrawal

	Annual rate/100 pts	NNH/y
WITHDRAWAL	↑ **1.16** [0.56-1.76]	**86**

- Similar rates reported with active treatment and placebo ~10-30%
- Dizziness, depression, cold extremities, fatigue
  - "marginally" more common in treatment groups

AUTHORS CONCLUSION

- “firm evidence shows that long term β blockade remains effective and well tolerated treatment that reduces mortality and morbidity in unselected patients after MI”
- β blockade has comparatively large effect to newer treatments in reducing mortality
- Most evidence for propranolol, timolol, metoprolol

STRENGTHS

- Summary of post-MI RCTs up to 1997
- Separate analysis of longer (>6 month) trials
- Random effects model

LIMITATIONS

- Mean publication date 1982
- Mean f/u 18 mos
- Funded by SmithKline Beecham - role not explicit
- No evaluation of risk of bias in individual studies
- Different definitions and reporting of withdrawal between trials

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

American Heart Association®

Effects of treatment on outcome in mildly symptomatic patients with ischemia during daily life. The Atenolol Silent Ischemia Study (ASIST)

C J Pepine, P F Cohn, P C Deedwania, R S Gibson, E Handberg, J A Hill, E Miller, R G Marks and U Thadani

Circulation. 1994;90:762-768

STUDY DESIGN

D	P, R, MC, DB, f/u 10.4 months (1990)
P	Mean age 64y, ~86% men, ~70% ASA Documented CAD (>50% stenosis coronary angiography or previous MI or 2 positive stress tests) AND transient ischemia (+ stress test within 6 mos) AND ≥2 asymptomatic ischemic episodes or 1 episode ≥ 5 min over 48h period during placebo lead-in *Excluded*: ACS within 3 months, class III+ angina, HF
I	Atenolol 100mg po daily (titrated to 50mg if side effects)
C	placebo
O	Death, resusc VT/VF, NF MI, hosp for UA, angina requ tx, revasc

RESULTS

	Atenolol (n=152)	Placebo (n=154)	RR [95% CI]
PRIMARY OUTCOME	17	39	↓ **0.44** [0.26-0.75]
Death, NF MI, VT/VF, hospitalization	7	13	0.55 [0.22-1.33]
Aggravation of angina	9	26	↓ **0.35** [0.17-0.72]
Bradycardia (%)	6.6	0	↑ **P=0.001**

AUTHORS CONCLUSIONS

- β-blockers reduce risk of adverse outcomes for patients with asymptomatic daily life ischemia
- β-blockers decrease frequency, duration, occurrence of daily life (asymptomatic) ischemia
- Absence of ischemia at wk 4 + age 60-69 increased favourable outcome at 1 year

STRENGTHS

- ITT analysis
- Adjustment for multiple comparisons

LIMITATIONS

- Early termination, f/u 10.4 mos
- Limited applicability
- Underpowered to demonstrate clear benefit on survival and MI
- No information re: statin, ACE-I use

The New England
Journal of Medicine

VOLUME 339 AUGUST 20, 1998 NUMBER 8

EFFECT OF BETA-BLOCKADE ON MORTALITY AMONG HIGH-RISK AND LOW-RISK PATIENTS AFTER MYOCARDIAL INFARCTION

STEPHEN S. GOTTLIEB, M.D., ROBERT J. MCCARTER, SC.D., AND ROBERT A. VOGEL, M.D.

STUDY DESIGN

D	MC, retrospective observational cohort, f/u 24mos (1994)
P	N = 201 752 (from Cooperative Cardiovascular Project database) Mean age 74y, 54% male, 83% ASA, 30% ACE-I Discharged after acute MI
I	BB prescribed at discharge
C	No beta-blocker at discharge
O	Mortality

RESULTS –Death

	BB (n=69,153)	No BB (n=132,599)	RR [95% CI]	ARR
Patients w/o complications (%)	14.4	23.9	**0.6** [0.57-0.63]	**9.5** **NNT 10.5**

- ↓ mortality in all subgroups
  - e.g. age < 70, black race, EF ≥ 50%, non-Q-wave infarction, asthma/COPD, diabetes

AUTHORS CONCLUSIONS

- Post-MI patients prescribed β-blockers at discharge have 40% lower mortality rate compared to those not prescribed β-blockers
  - All patient subgroups had similar benefit

STRENGTHS

- Controlled for covariates that differed between groups
- Evidence for previously unstudied groups

LIMITATIONS

- No adjustment for multiple subgroup analyses
- Limited generalizeability – patient population with Medicare insurance
- Specific BB used not identified
- Observational design → unmeasured confounders
- Pre-ACEI & statin era

Beta-Blocker Prescription Among Japanese Cardiologists and Its Effect on Various Outcomes

Takahide Kohro, MD; Dobun Hayashi, MD**; Tsutomu Yamazaki, MD*;
Ryozo Nagai MD**; The JCAD Investigators

(*Circ J* 2010; **74:** 962–969)

STUDY DESIGN

D	MC, prospective observational cohort, f/u 2.7y (2000)
P	N = 13 812, 76% male, mean age 65y CAD diagnosis (≥75% stenosis ≥ 1 coronary artery) →21% acute MI, 28% history of MI, 15% UA -44% statin, 37% ACEI, 16% ARB, 61% antithrombotic
I	Beta-blockers at discharge
C	No beta-blocker at discharge
O	1°: All-cause death + cerebrovascular events (cardiac, cerebral, vascular) 2°: components of composite

β-blocker vs. No β-blocker

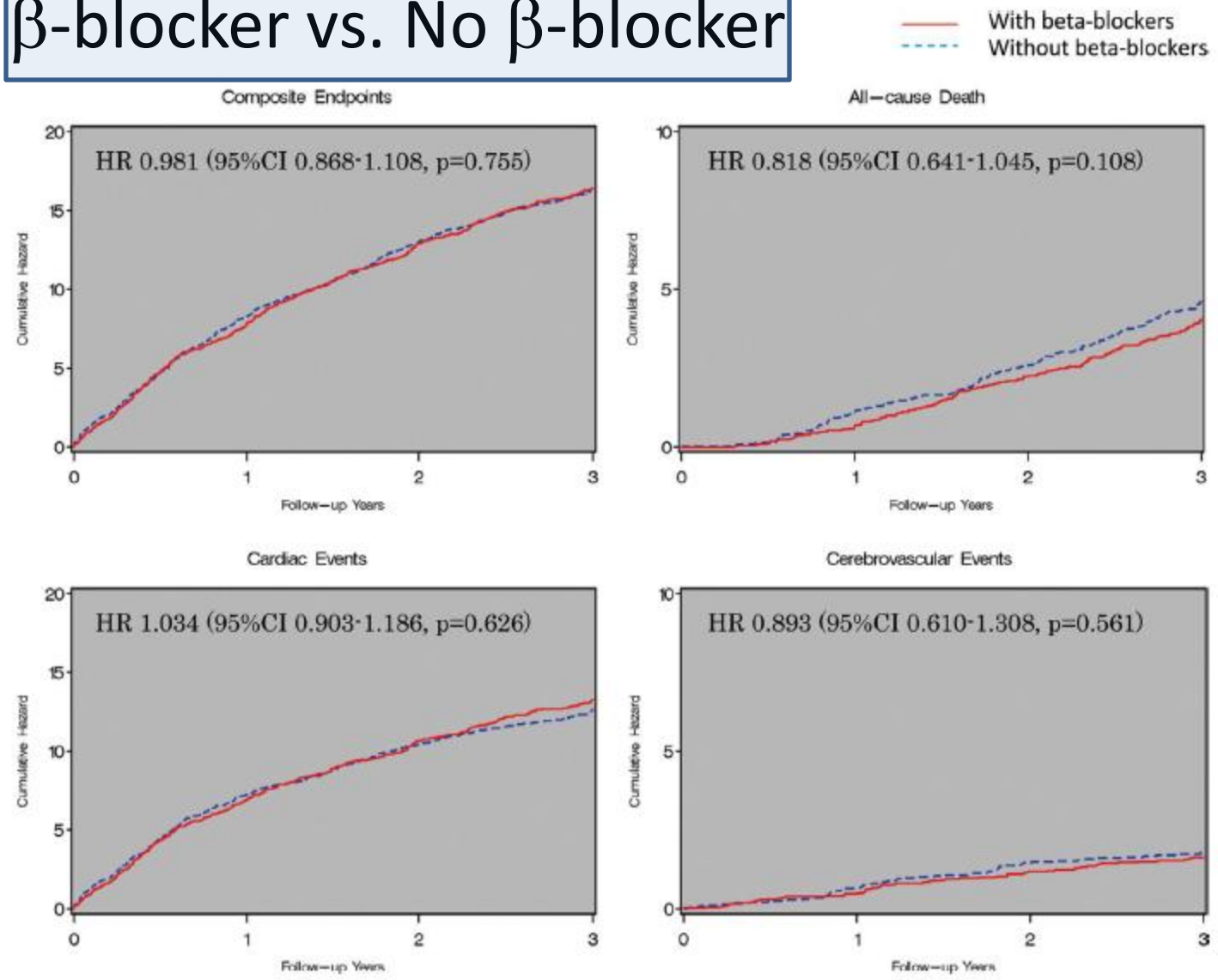


Figure 3. Patients who were taking β-blockers were matched with those who were not taking β-blockers based on propensity scores calculated by logistic regression. Kaplan-Meier analysis was performed on the 2 groups with various endpoints. HR, hazard ratio; CI, confidence interval.

Lipophilic β-B vs. Hydrophilic β-B

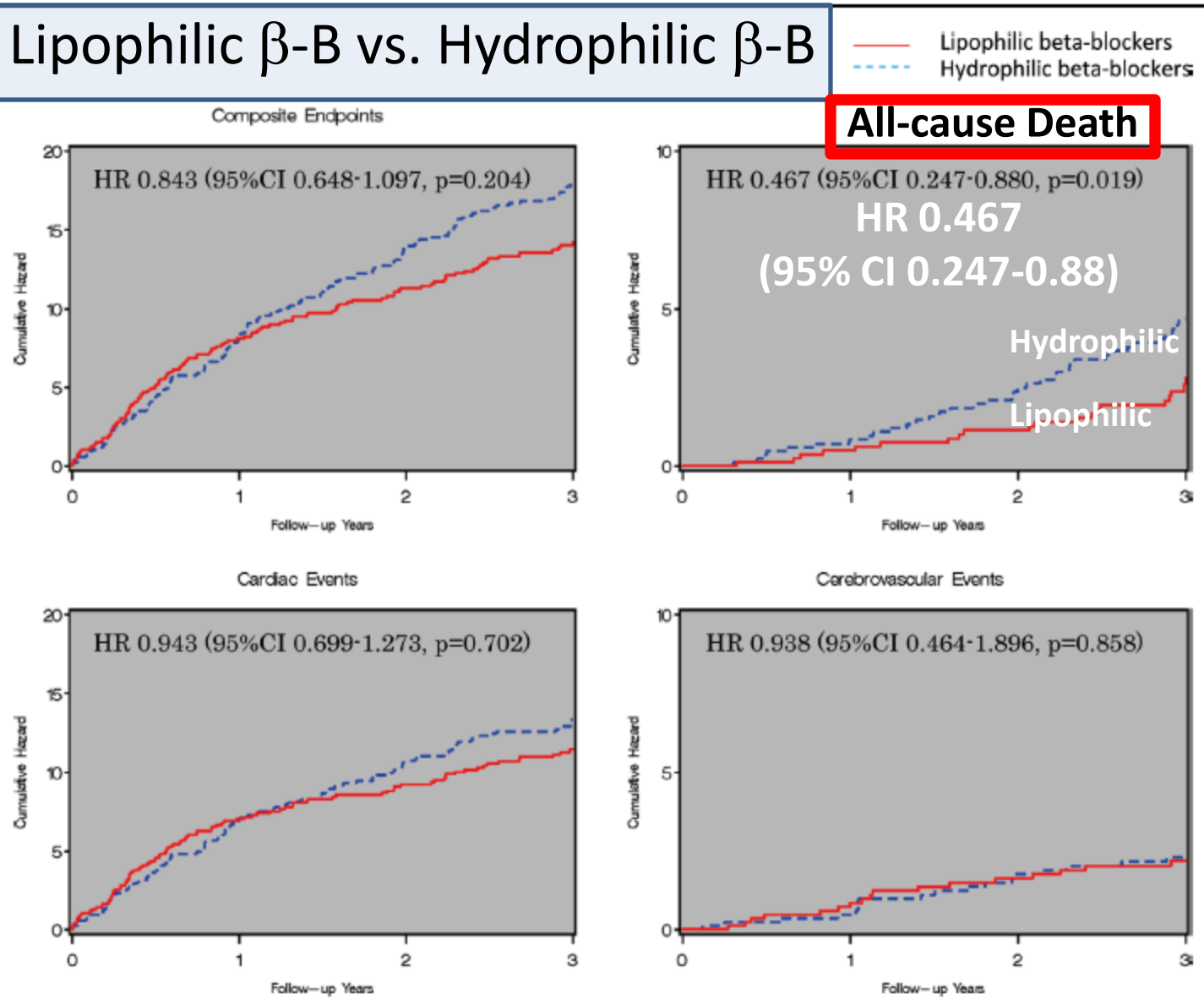


Figure 4. Patients who were taking lipophilic β-blockers were matched with those who were taking hydrophilic β-blockers based on propensity scores calculated by logistic regression. Kaplan-Meier analysis was performed on the 2 groups with various endpoints. HR, hazard ratio; CI, confidence interval.

AUTHORS CONCLUSIONS

- β-blocker continuation rate relatively high, suggesting good tolerability
- No clear benefit of β-blockers for various outcomes
- Lipophilic β-blockers may be better choice than hydrophilic β-blockers for mortality benefits

STRENGTHS

- More recent data
- Propensity score matched analysis
- High continuation rate
- F/u 2.7y

LIMITATIONS

- Mixed diagnoses (not exclusively post-MI)
- Observational design
- Not all patients matched, ?power calculation
- Adverse effects not reported
- ITT analysis based on BB use at time of discharge

SUMMARY

	OUTCOME
Pepine (1994)	↓ Death, resusc VT/VF, NF MI, hosp for UA, angina requ tx, revasc
Gottlieb (1998)	↓ Death
Freemantle (1999)	↓ Death & re-infarction
Kohro (2010)	↔ Death
Bangalore (2012)	↔ CV events/death

MY CONCLUSION

- Current evidence suggests no benefit of β-blockade beyond 2 years
- Potential for adverse effects & unnecessary costs with continued β-blocker therapy

$\Rightarrow$ Recommend discontinuing β-blocker at 2y post-MI if normal LVEF and no anginal symptoms

Questions