Welcome to the WSU Department of Medicine Residency Journal Club

Applying “best evidence” to the care of individual patients

Caveats: I am not a statistician nor is this a course in statistics. We will, however, be exploring some of the important statistical concepts which will underlie your ability to make well-informed decisions about the validity and utility of medical evidence.

While these lectures may help clarify your understanding about the topics presented, they in no way substitute for more formal study of statistics, evidence-based practice and clinical research. I encourage you to pursue your interest in these areas through course work or self study – you’ll find selected resource information on the web page.

Robert Burack, MD, MPH

Guilt by Association

Or, could your primary suspect simply have been an innocent bystander?

Today's patient

- Mr. Jones is a 68 year old man who presents for pre-operative evaluation in advance of elective hip replacement surgery
- His past medical history includes stable angina, hypertension and hyperlipidemia (all well-controlled) without previous MI or revascularization), CHF, vascular disease, diabetes or smoking.
- His physical exam reveals BP of 126/78 with no evidence of cardiovascular disease (and is otherwise unremarkable)
- His current medications include ACE inhibitor, statin, aspirin
- Do you recommend perioperative beta-blockade?
  - ❑ *Yes - it carries a Class IIa AHA guideline recommendation*
  - ❑ *Yes - he has documented angina and 2 risk factors*
  - ❑ *No – it's unnecessary and potentially harmful*
  - ❑ *Let's consult cardiology*

US and European guidelines would support at least strong consideration of perioperative β-blockade

Table 1 Guideline recommendations for initiation of perioperative β-blockade

Patient group	2009
ACCF/AHA guidelines	
Vascular surgery and ischaemia on preoperative testing	Class IIa with dose titration
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ESC guidelines	
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High-risk surgery	Class I, with dose titration
Intermediate-risk surgery	Class IIa, with dose titration

And in this study the risk of an adverse cardiovascular outcome was lower among patients receiving perioperative β-blockade

Research

Original Investigation

Association of β-Blocker Therapy With Risks of Adverse Cardiovascular Events and Deaths in Patients With Ischemic Heart Disease Undergoing Noncardiac Surgery

A Danish Nationwide Cohort Study

Charlotte Andersson, MD, PhD; Charlotte Mérie, MD; Mads Jørgensen, MB; Gunnar H. Gislason, MD, PhD; Christian Torp-Pedersen, MD, DSc; Charlotte Overgaard, PhD; Lars Køber, MD, DSc; Per Føge Jensen, MD, PhD, MHM; Mark A. Hlatky, MD

IMPORTANCE Clinical guidelines have been criticized for encouraging the use of β-blockers in noncardiac surgery despite weak evidence. Relevant clinical trials have been small and have not convincingly demonstrated an effect of β-blockers on hard end points (ie, perioperative myocardial infarction, ischemic stroke, cardiovascular death, and all-cause death).

OBJECTIVE To assess the association of β-blocker treatment with major cardiovascular adverse events (MACE) and all-cause mortality in patients with ischemic heart disease undergoing noncardiac surgery.

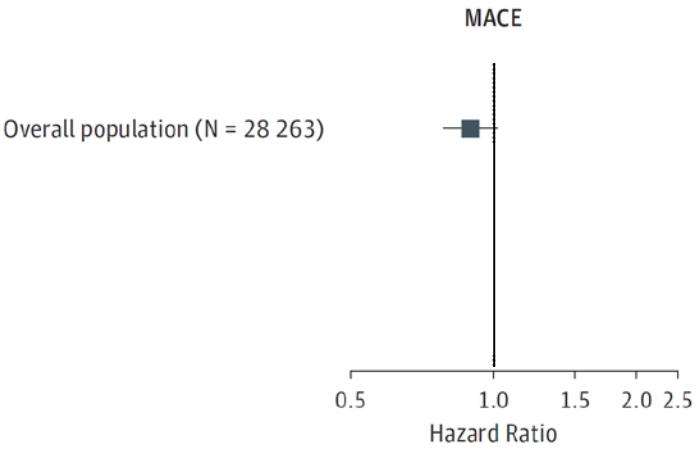
DESIGN, SETTING, PARTICIPANTS, AND EXPOSURE Individuals with ischemic heart disease with or without heart failure (HF) and with and without a history of myocardial infarction undergoing noncardiac surgery between October 24, 2004, and December 31, 2009, were identified from nationwide Danish registries. Adjusted Cox regression models were used to calculate the 30-day risks of MACE (ischemic stroke, myocardial infarction, or cardiovascular death) and all-cause mortality associated with β-blocker therapy.

MAIN OUTCOMES AND MEASURES Thirty-day risk of MACE and all-cause mortality.

RESULTS Of 28 263 patients with ischemic heart disease undergoing surgery, 7990 (28.3%) had HF and 20 273 (71.7%) did not. β-Blockers were used in 4262 (53.3%) with and 7419 (36.6%) without HF. Overall, use of β-blockers was associated with a hazard ratio (HR) of 0.90 (95% CI, 0.79-1.02) for MACE and 0.95 (0.85-1.06) for all-cause mortality. Among patients with HF, use of β-blockers was associated with a significantly lower risk of MACE (HR, 0.75; 95% CI, 0.70-0.87) and all-cause mortality (0.80; 0.70-0.92), whereas among patients without HF, there was no significant association of β-blocker use with MACE (1.11; 0.92-1.33) or mortality (1.15; 0.98-1.35) ($P < .001$ for interactions). Among patients without HF, β-blockers were also associated with a lowered risk among those with a recent myocardial infarction (<2 years), with HRs of 0.54 (95% CI, 0.37-0.78) for MACE and 0.80 (0.53-1.21) for all-cause mortality ($P < .02$ for interactions between β-blockers and time period after myocardial infarction), but with no significant association in the remaining patients. Results were similar in propensity score–matched analyses.

CONCLUSIONS AND RELEVANCE Among patients with ischemic heart disease undergoing noncardiac surgery, use of β-blockers was associated with lower risk of 30-day MACE and mortality only among those with HF or recent myocardial infarction.

Figure 1. Hazard Ratios Associated With β-Blockers in Different Subgroups



EBM journal club (R. Burack, 2014)

So if you withhold β-blockade are you guilty as charged or could effect modification and confounding provide you an alibi?

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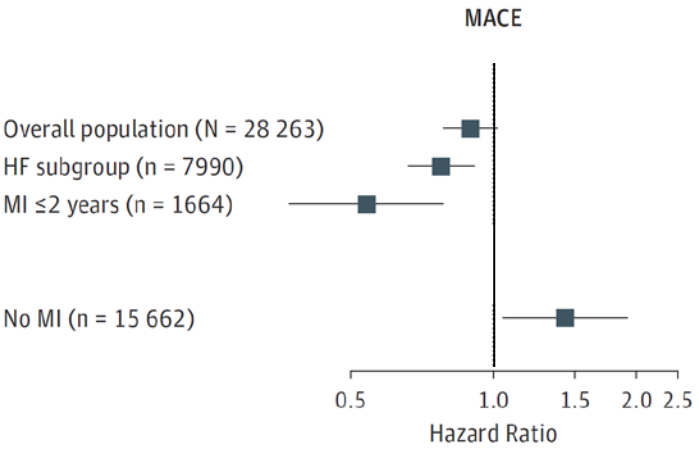

The effects associated with β-blockers differed in patients with and without heart failure (HF) (*P* < .001 for interactions between β-blockers and HF for both end points). Among the subgroup without HF, the hazard ratios associated with β-blockers were further dependent on a history of MI and time elapsed since the most recent MI (for interaction between β-blockers and MI categories,

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EBM journal club (R. Burack, 2014)

Today's objectives

- ***Effect modification***
  - Do effects differ among subgroups
  - If important, how do we assess and interpret these differences?
- ***Confounding***
  - Could one "apparent" risk factor simply be serving as a marker for another which is the "actual" cause?
  - How do we take these relationships into account?

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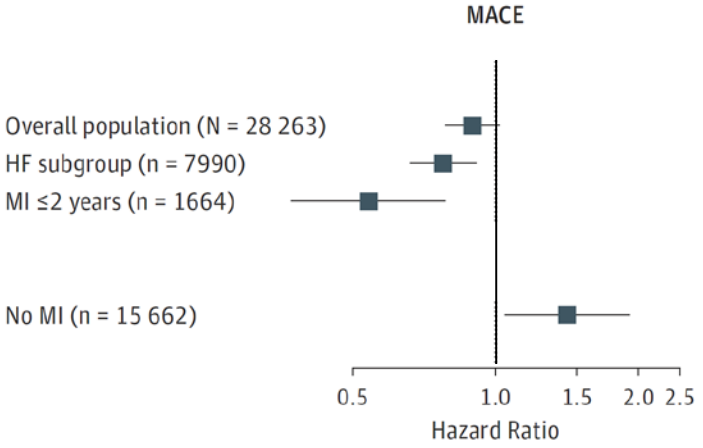

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And today's challenge - our study is not a randomized controlled trial

Can you believe what you've read? (validity)
▪ Study design ▪ Treatment assignment and delivery ▪ Outcome assessment ▪ Analysis by intention to treat
What exactly was the observed effect? (reality)
▪ Effect size (estimate and 95% CI) ▪ Role of chance in observation (p-value and power)
Does it really matter? (utility)
▪ Applicable and relevant to patient ▪ Balance between potential benefits and harms

- Rather, it is a retrospective cohort study in which treatment is "clinically" not randomly assigned
- If the treatment groups are not randomly assigned and thus well-balanced can we trust the study results?
- What can we do to improve the likelihood that any conclusions we draw based on the results are "true"?

Study overview

Objective

- "To assess the association of β-blocker treatment with major cardiovascular adverse events (MACE) and all-cause mortality in patients with ischemic heart disease undergoing noncardiac surgery."

Design

- Retrospective cohort based upon nationwide Danish registries

Participants

- 28,263 Danish patients with ischemic heart disease undergoing noncardiac surgery between 2004-09, of whom 11,681 received and 16,582 did not receive β-blocker treatment

Intervention and measurements

Intervention

- Perioperative β-blocker treatment

Control

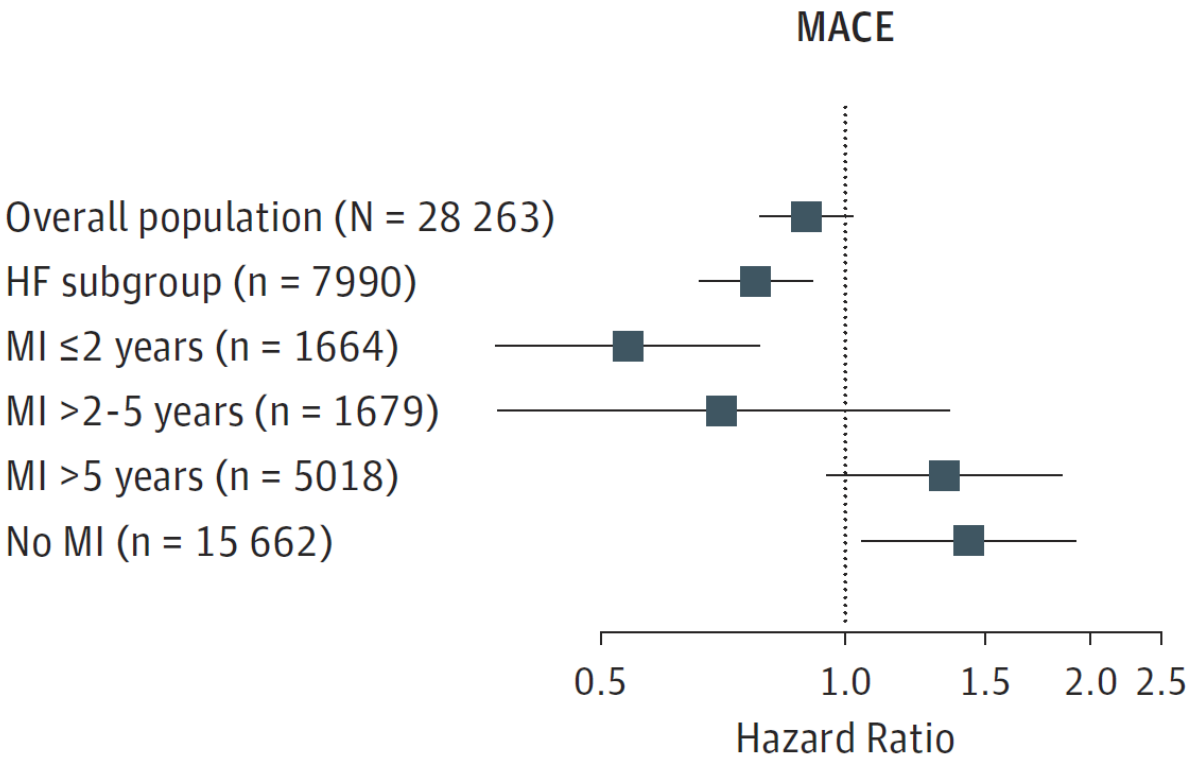
- Absence of perioperative β-blocker treatment

Measurements

- Thirty day risk of major adverse cardiovascular event
- Thirty day all-cause mortality

Summary of study results

Figure 1. Hazard Ratios Associated With β-Blockers



So, is β-blockade indicated for our patient who has angina and two risk factors and will be undergoing intermediate-risk surgery?

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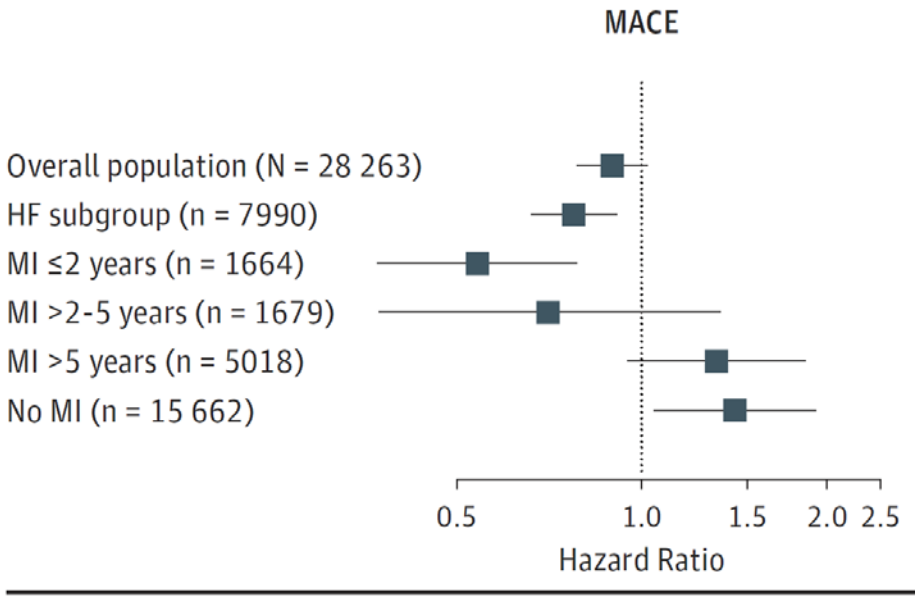

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To answer our question let's take a closer look at the data. Focusing on MACE and heart failure, do you see a pattern?

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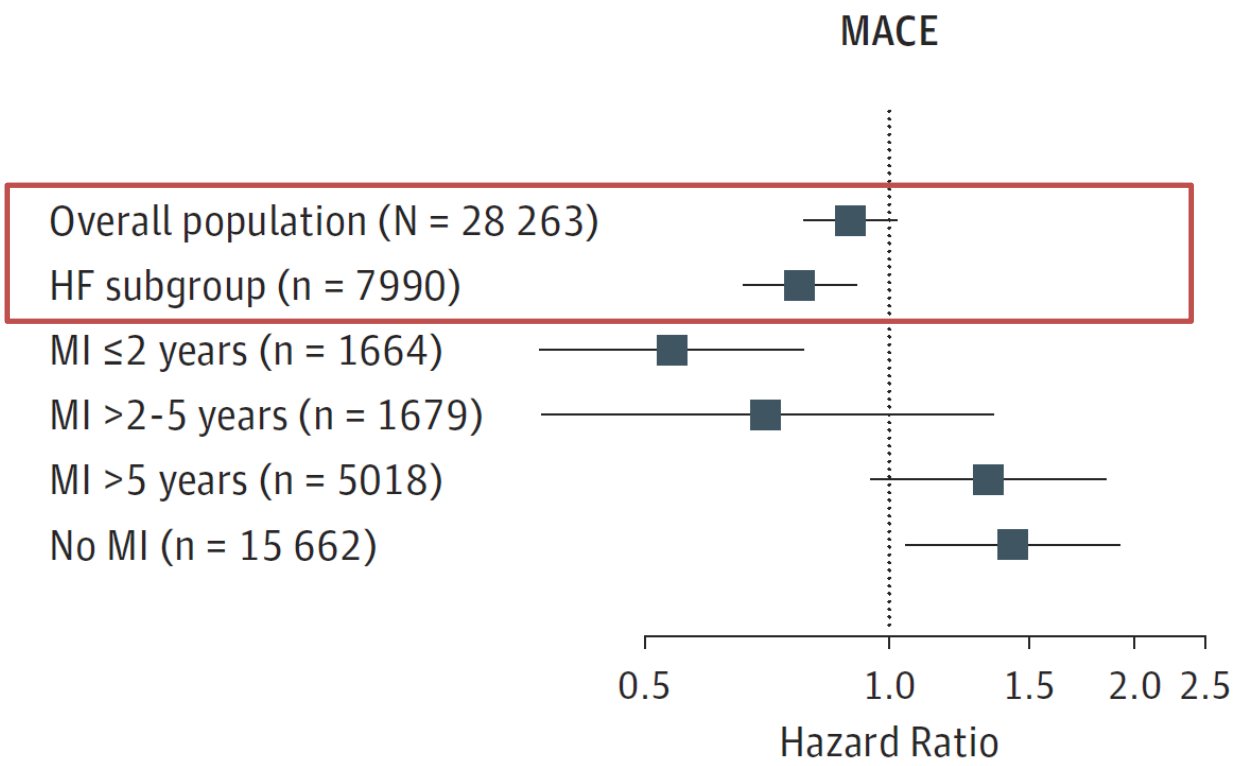
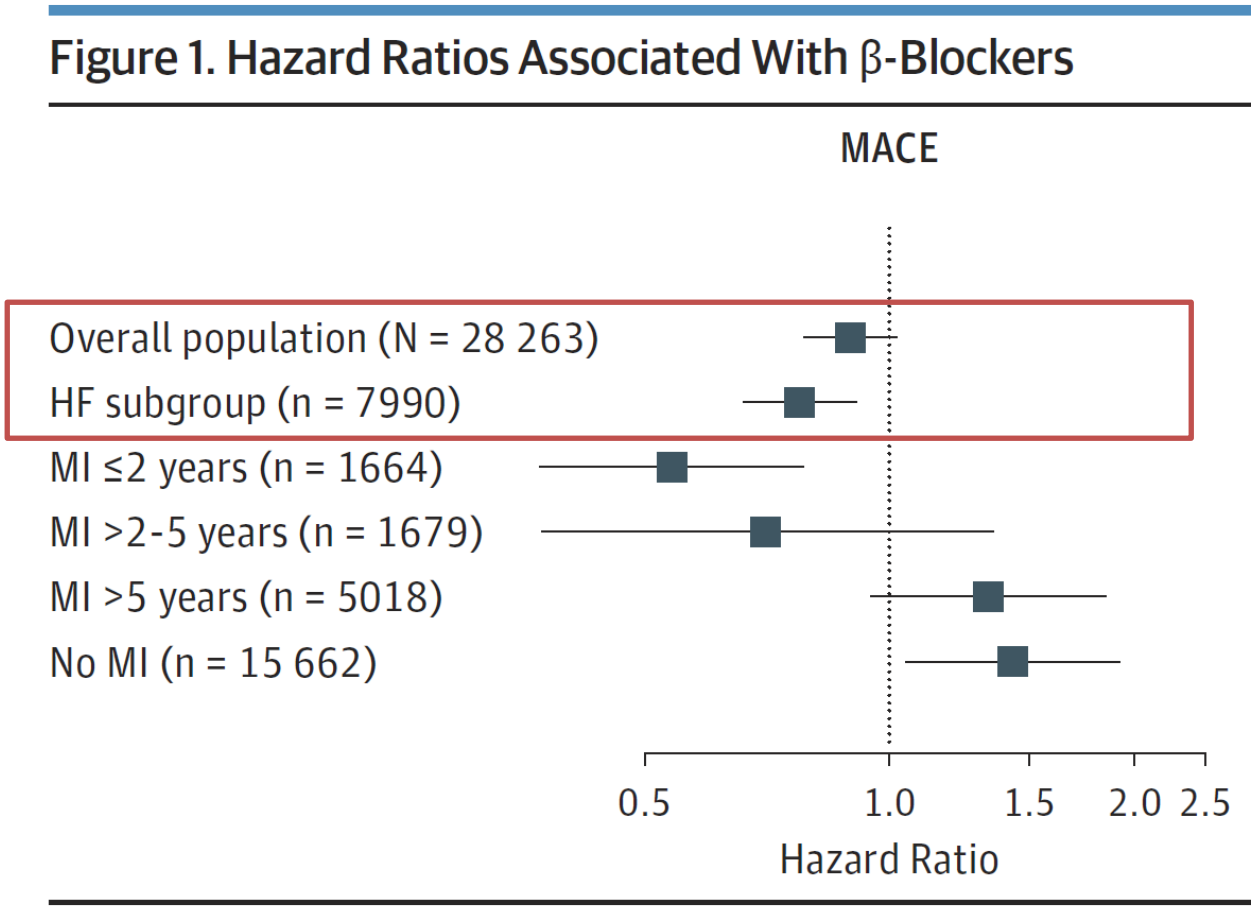
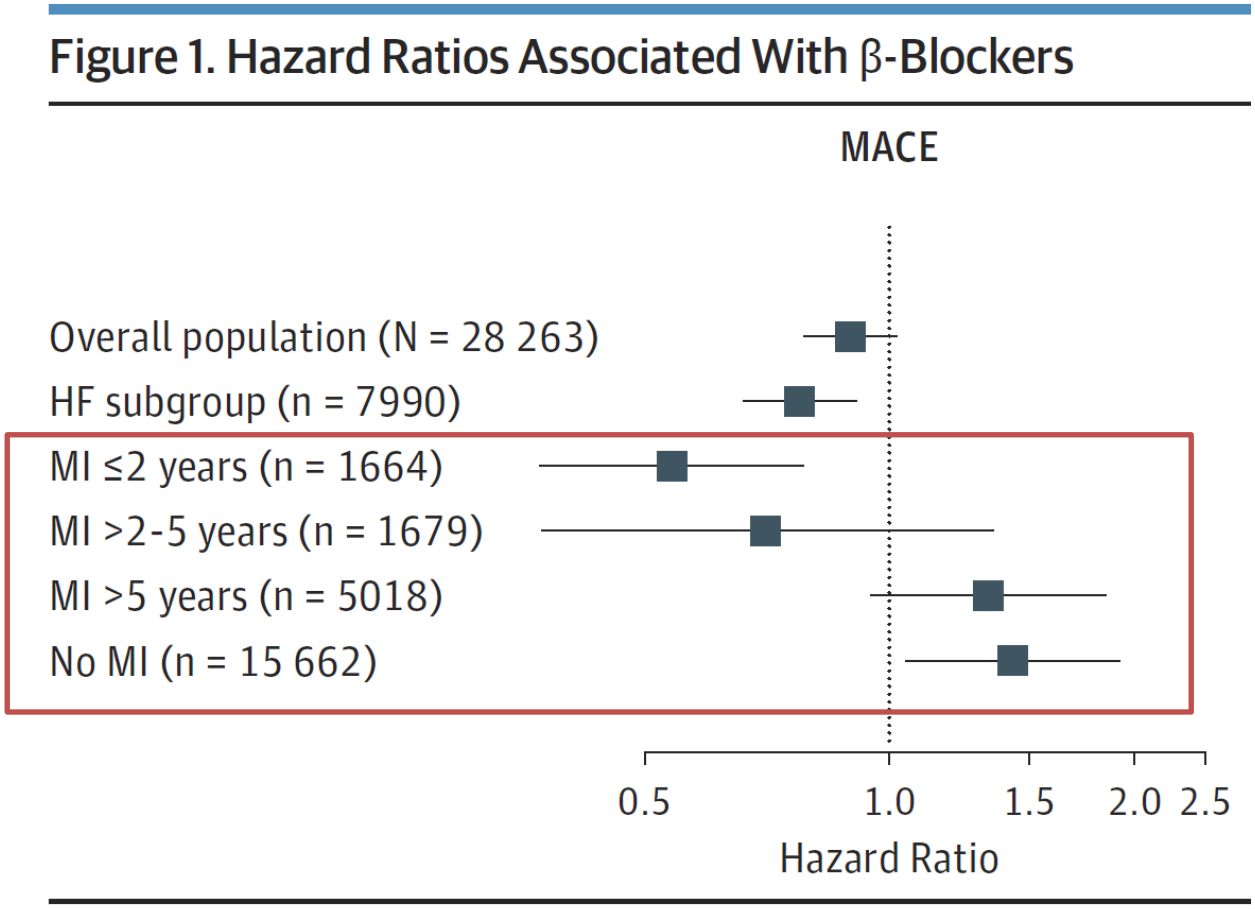


To answer our question let's take a closer look at the data. Focusing on MACE and heart failure, do you see a pattern?

Yes and it's called *effect modification* - the benefit of β-blockade seems greater in those with HF than in the population as a whole

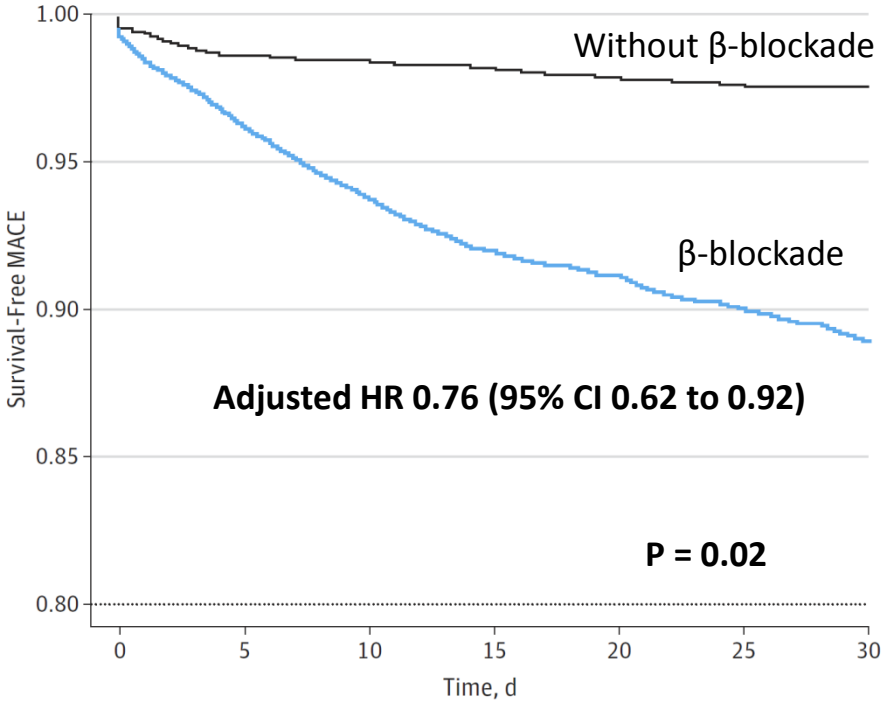


And the effect is even more dramatic if we examine MACE risk myocardial infarction history. β-blockade appears to substantially reduce risk among patients with a recent MI (≤2 years) while apparently *increasing* risk among those without a previous MI

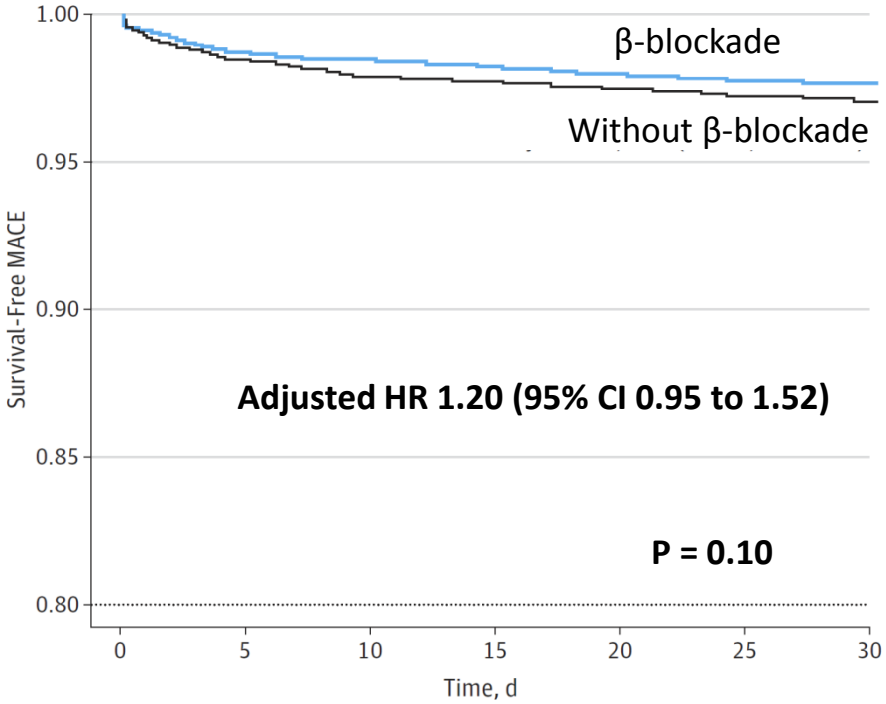


Here's another look at effect modification focusing on heart failure. Note that when effect modification is present there can be *no single summary measure* which describes a factor's "overall" effect. Does β-blockade reduce risk by 24% (HR 0.76) or increase it by 20% (HR 1.20)

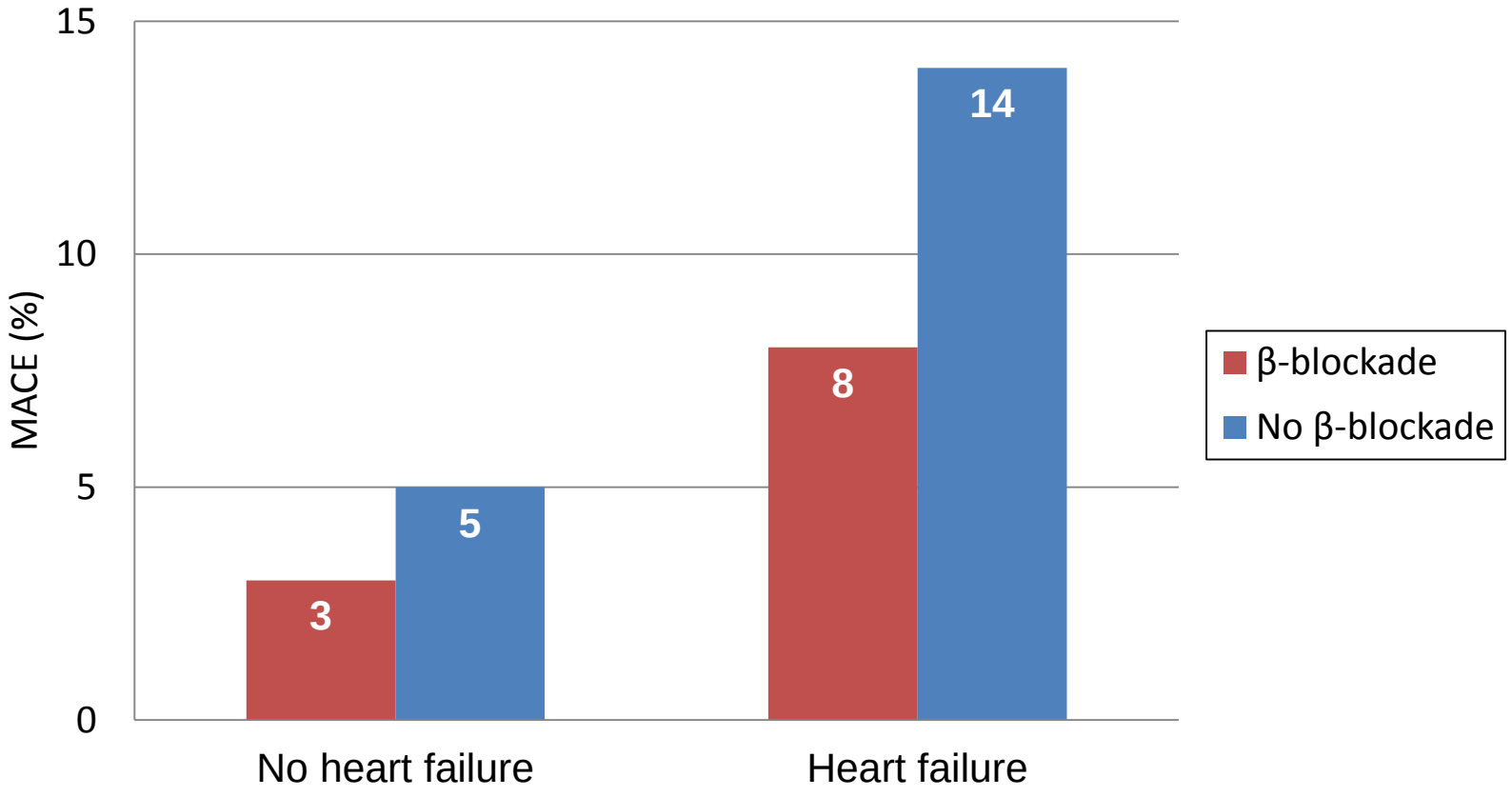
MACE risk for patients with HF



MACE risk for patients without HF



Let's use this bar chart to identify the contribution of effect modification to our study's results – where will we find it?



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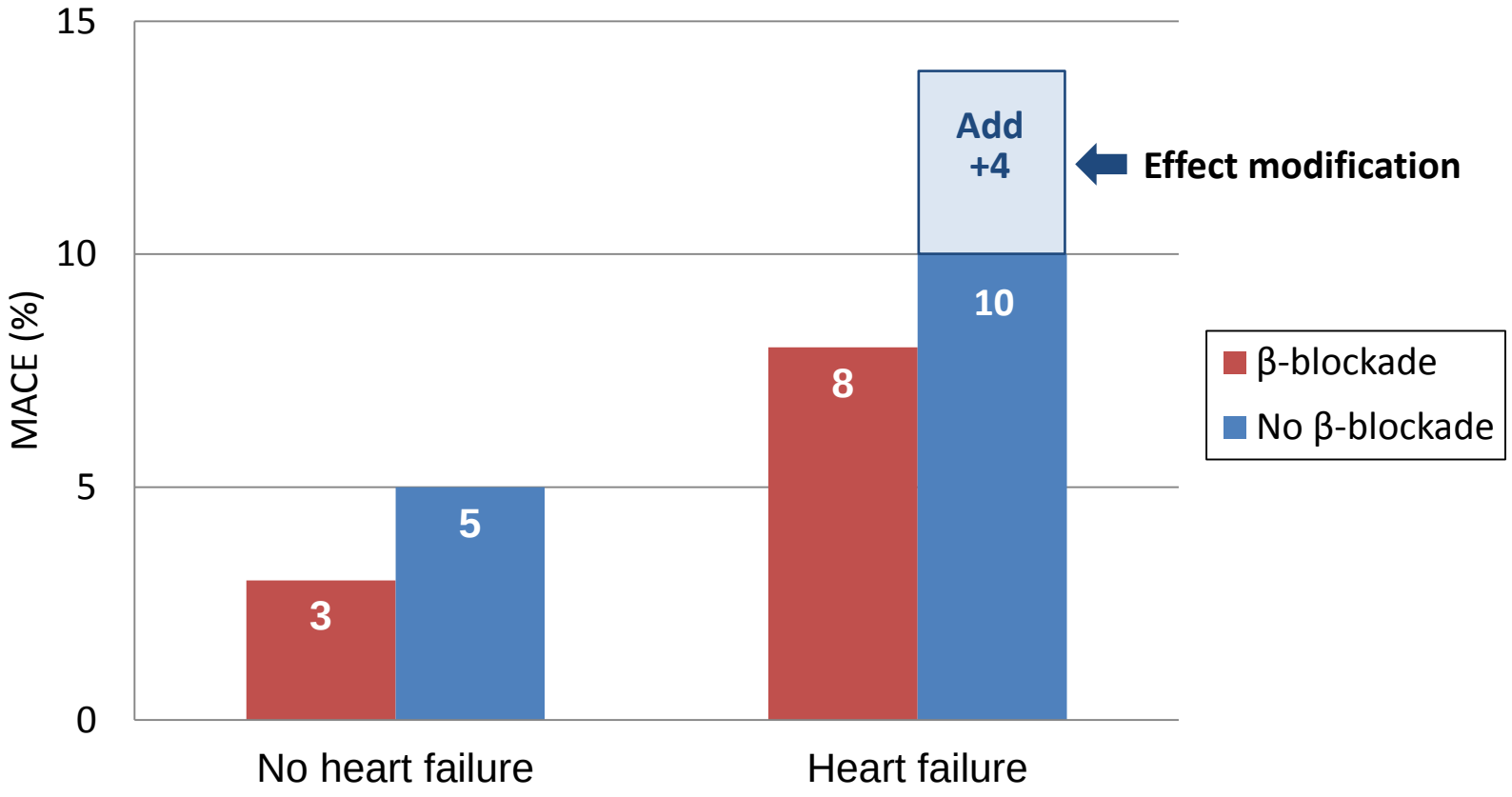
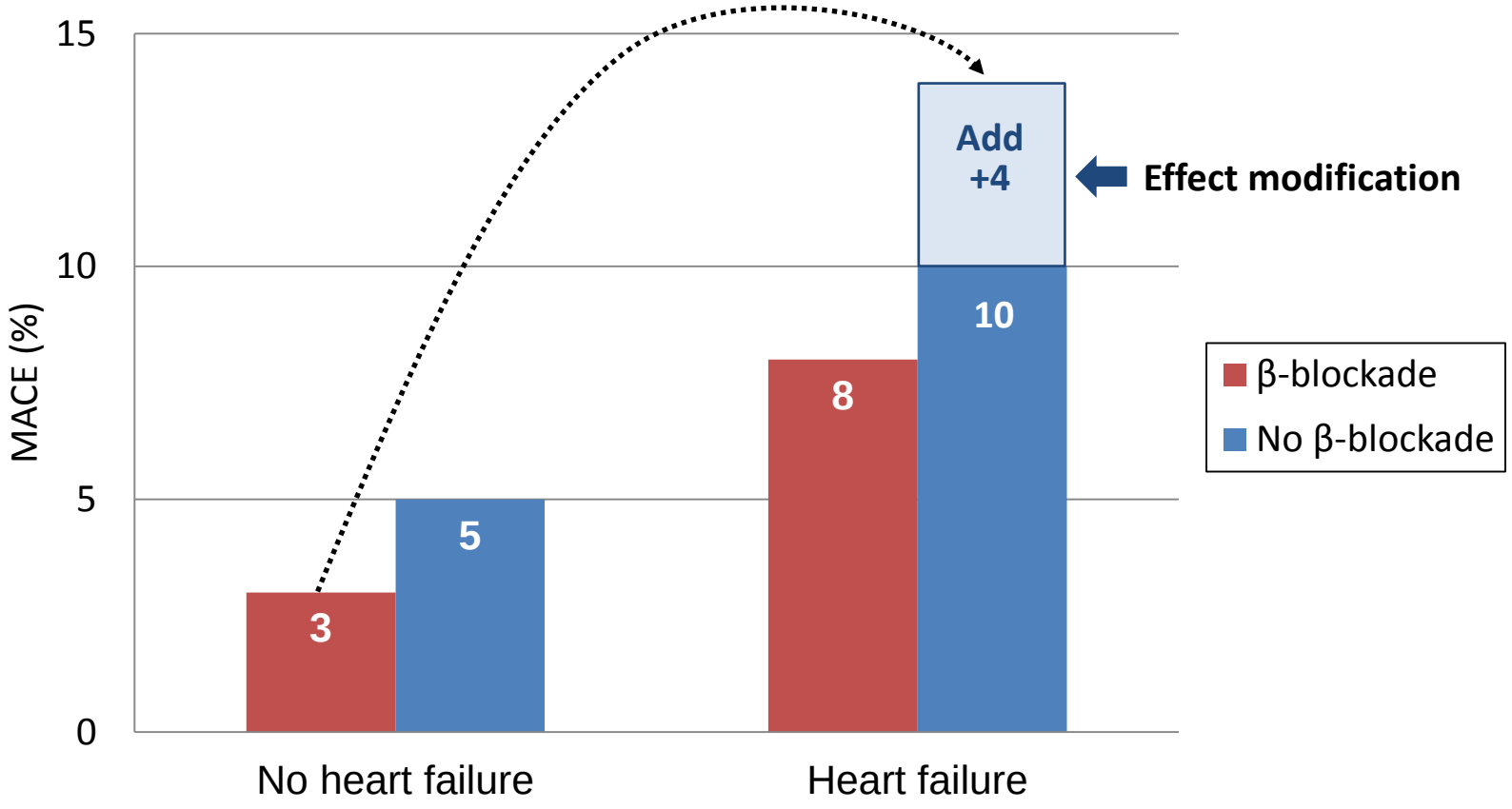
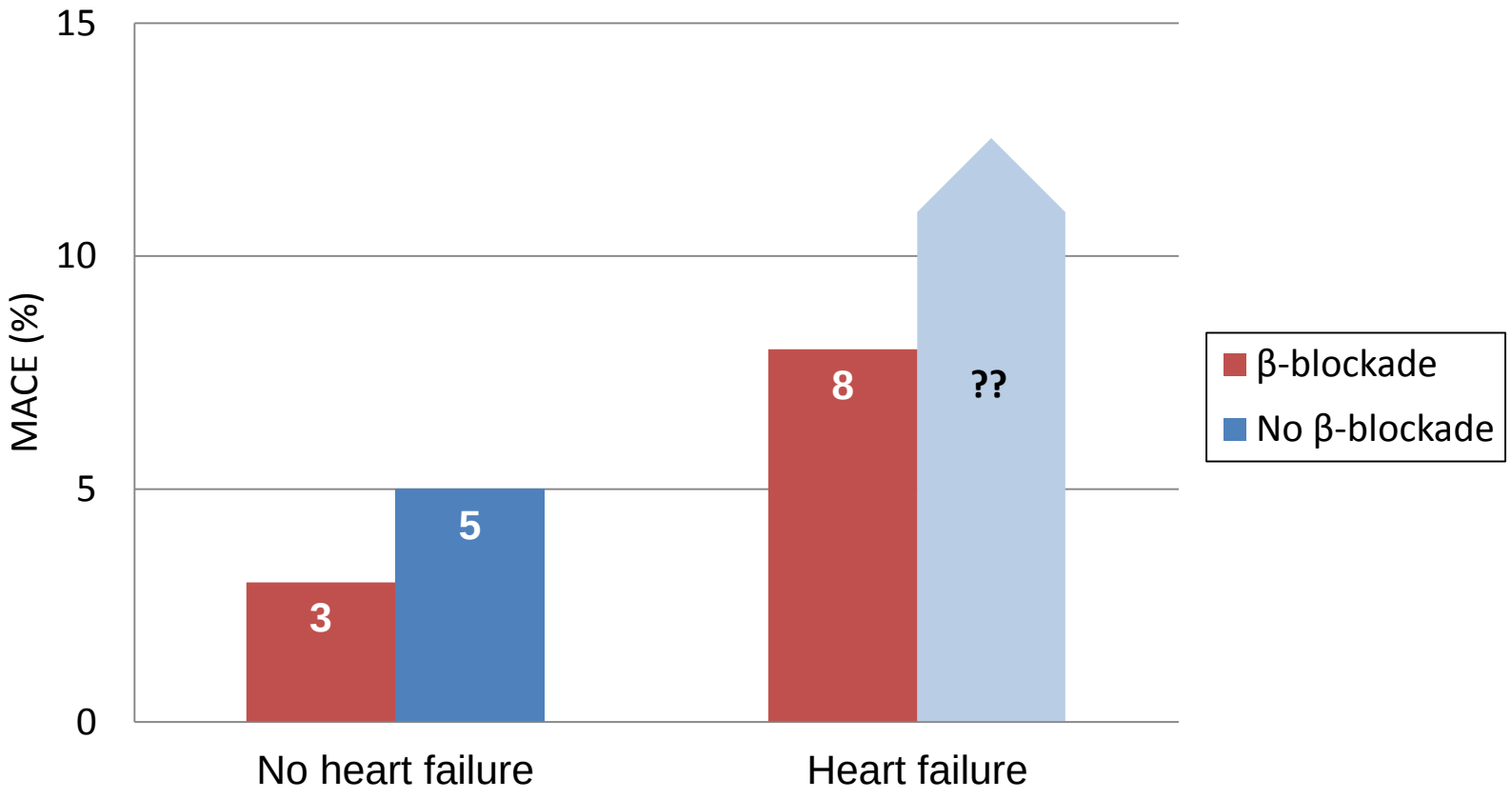


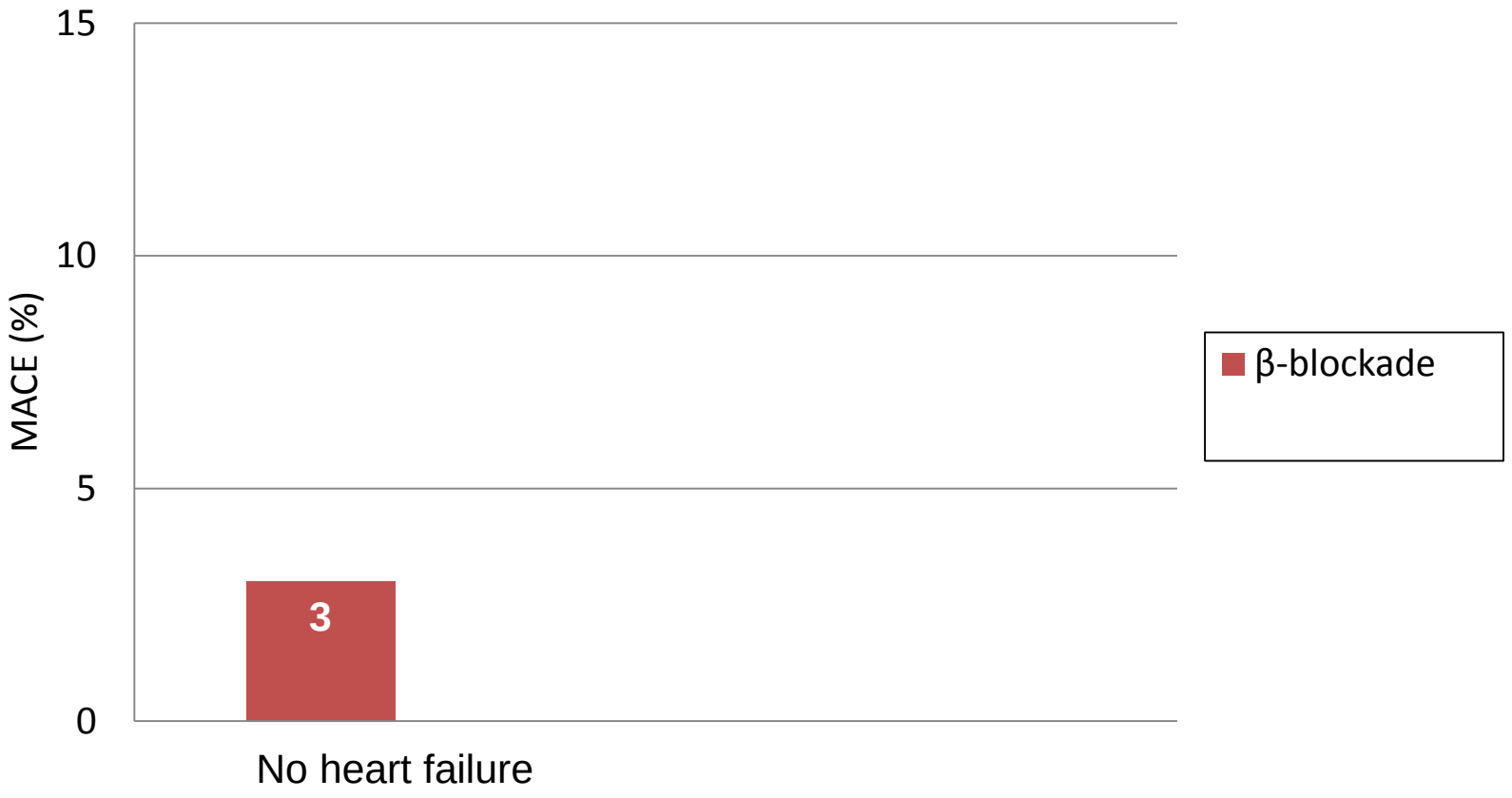
Another way to envision effect modification –
do you see the presence of effect modification in these results?
Here's a (large) hint, but the real question is how we got there.



To answer this question we'll ask another – what would we expect the MACE risk to be among heart failure patients who don't receive β-blockade?



We have two risk factors - heart failure and the omission of β-blockade. The baseline risk in their absence is 3%.



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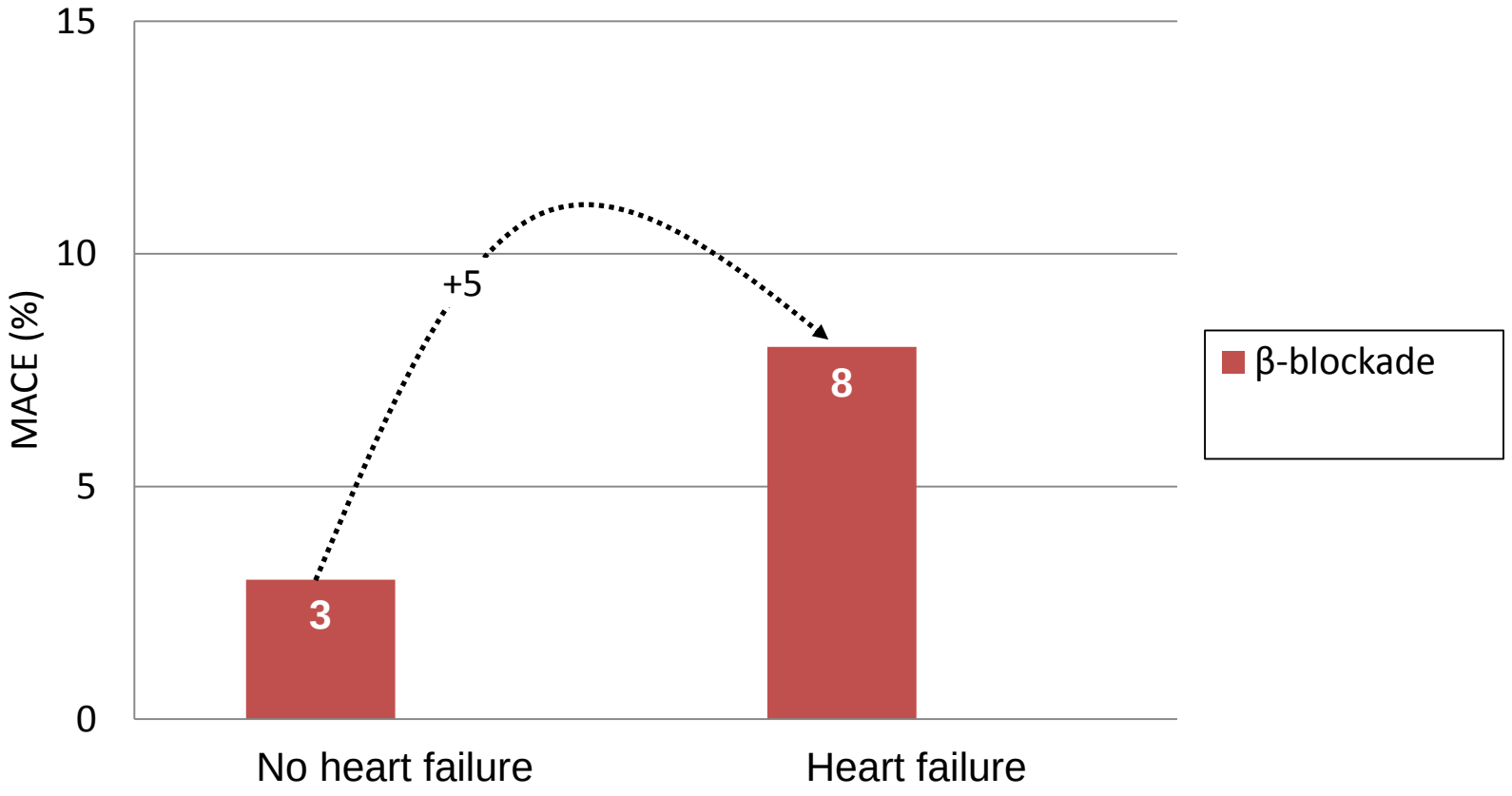
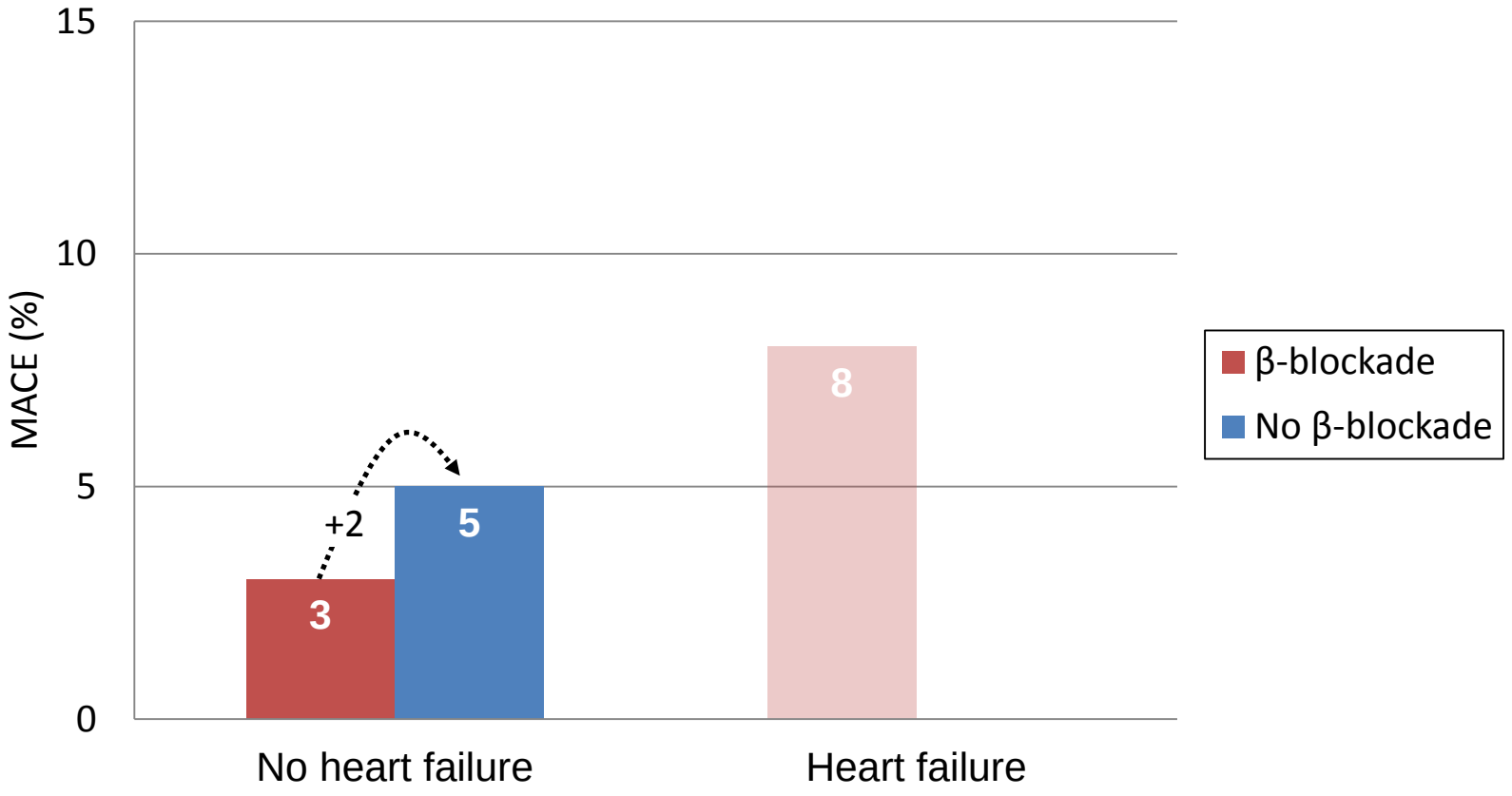
Heart failure adds 5% to risk even when β-blockade is provided

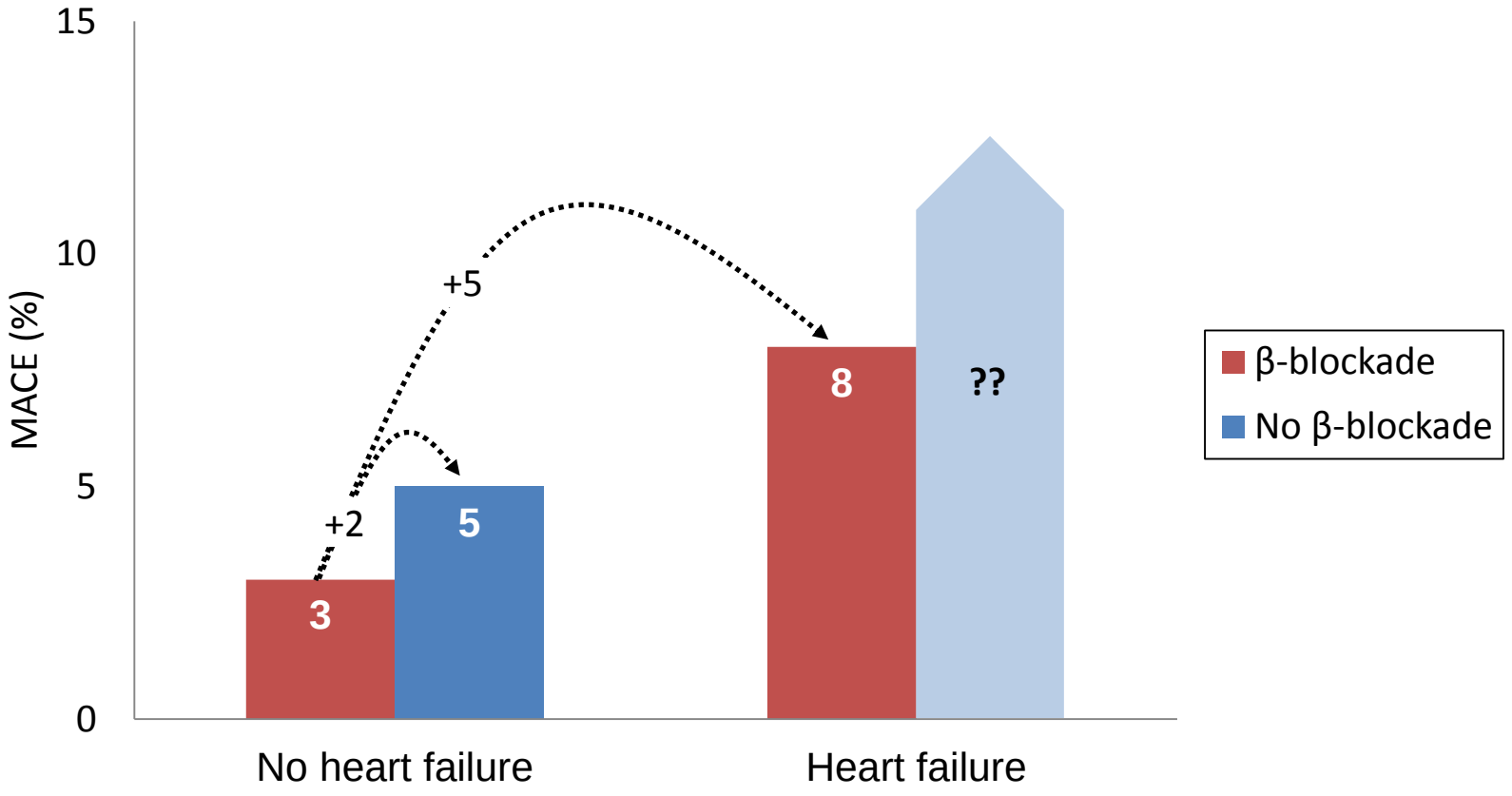


We have two risk factors - heart failure and the omission of β-blockade. The baseline risk in their absence is 3%. Heart failure adds 5% to risk even when β-blockade is provided

On the other hand, omitting β-blockade (in the absence of heart failure) adds its own 2% to the level of risk

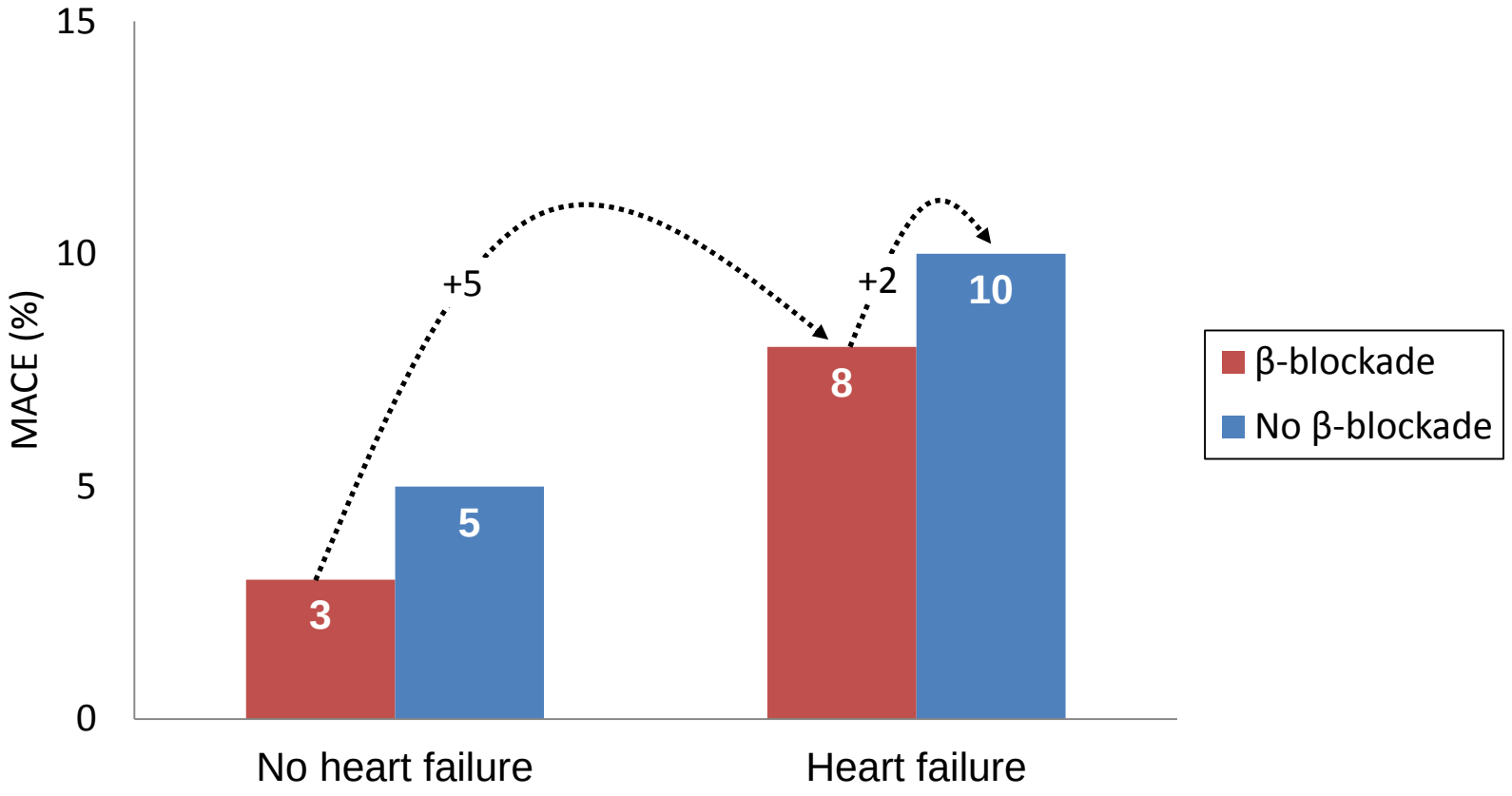


So, if HF by itself adds 5% to the baseline risk of 3% and omitting β-blockade adds its own 2%, what should we expect the level of risk to be among patients with HF who don't receive β-blockade?

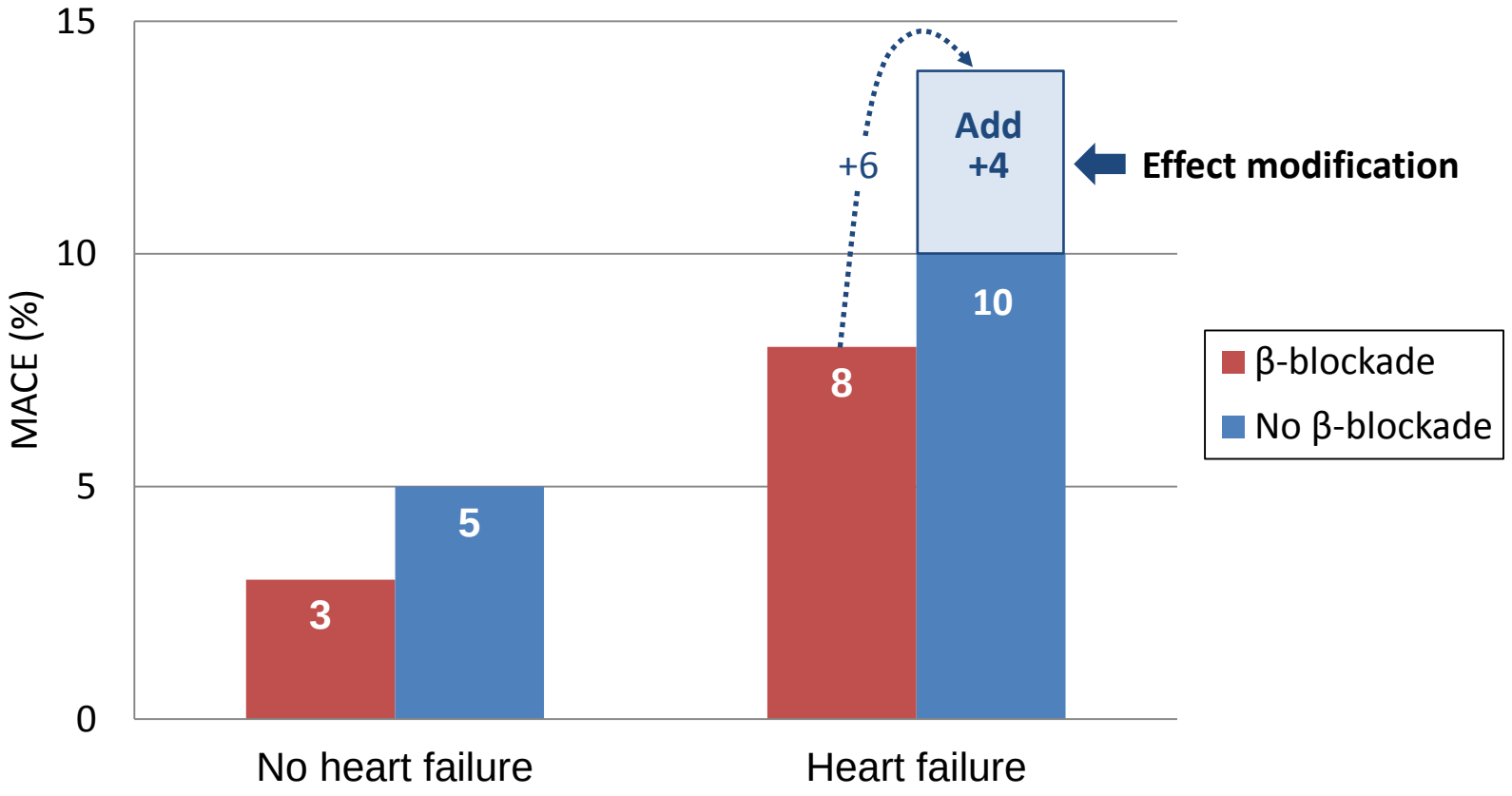


So, if HF by itself adds 5% to the baseline risk of 3% and omitting β-blockade adds its own 2%, what would we expect the level of risk to be among patients with HF who don't receive β-blockade?

How about 10% (3% baseline + 5% for HF + 2% if omit β-blockade)?



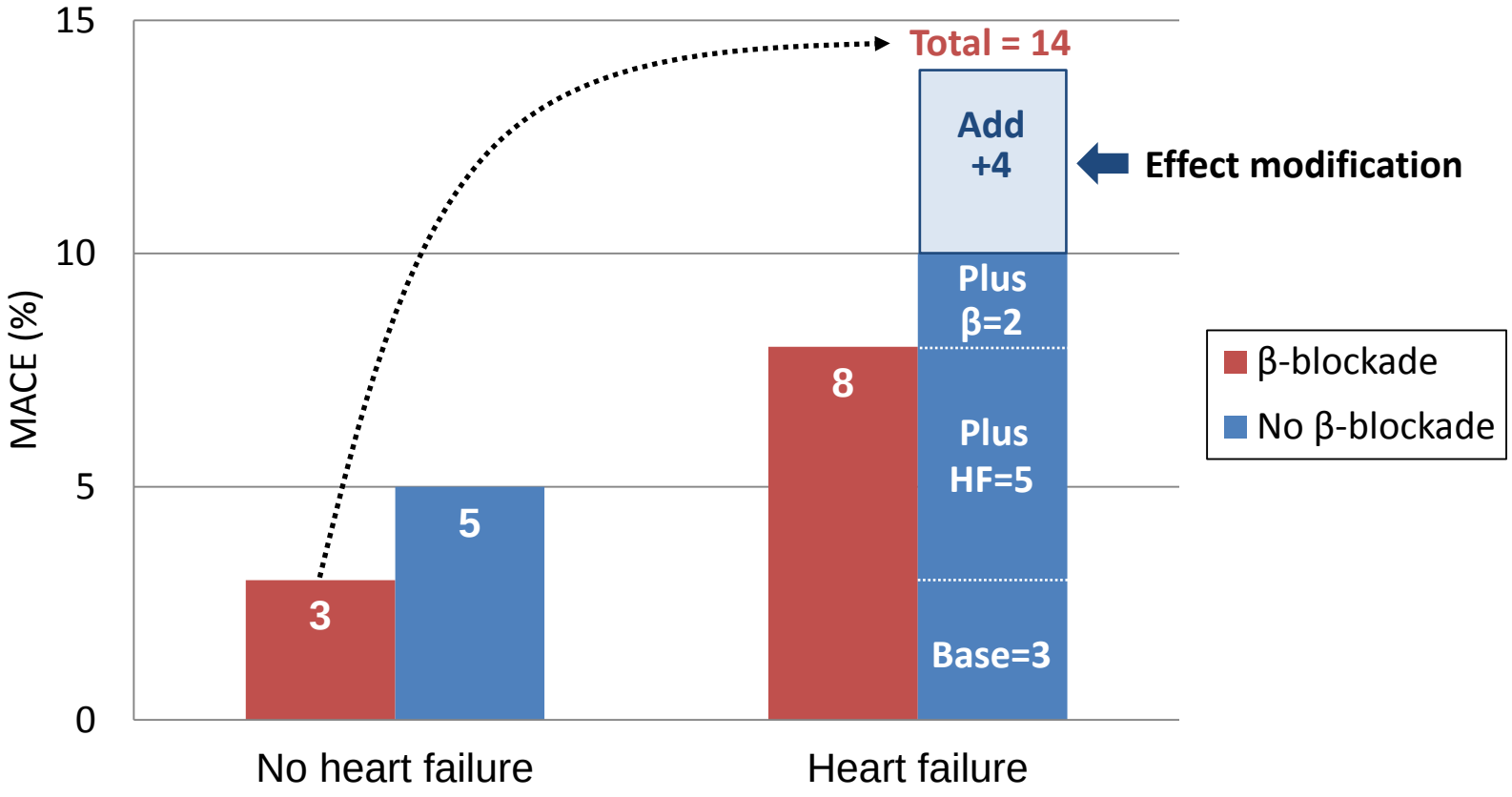
But that's not what we find – the observed risk is 14%, not 10%. The extra 4% arises from *effect modification* (statistical interaction). The joint effect of the two factors acting together (synergistically) exceeds what we'd expect based on their individual effects alone.



From the perspective of a statistical model, this extra effect is represented by the addition of a new term (the *interaction term*)

$$\text{Risk} = a + b_1(\text{HF}) + b_2(\beta\text{-blockade}) + b_3(\text{HF}*\beta\text{ blockade})$$

Risk (HF with β-blockade omitted) = 3 + 5 + 2 + 4 = 14



Break

We'll next move from effect modification to confounding – while both influence our interpretation of data they do in very different ways (and for different reasons)

Even if we take effect modification into account we still have another problem – since this isn't a randomized controlled trial the treatment groups are not balanced. Should we care?

Table 1. Baseline Characteristics

Characteristic	Heart Failure			No Heart Failure		
	β-Blockers (n = 4262)	No β-Blockers (n = 3728)	*P* Value for Difference	β-Blockers (n = 7419)	No β-Blockers (n = 12 854)	*P* Value for Difference
Age, mean (SD), y	73.4 (10.7)	76.1 (11.1)	<.001	68.8 (10.9)	68.8 (12.1)	.63
Male sex, No. (%)	2598 (61.0)	1981 (53.1)	<.001	4751 (64.0)	7505 (58.4)	<.001
Urgent surgery, No. (%)	1862 (43.7)	1912 (51.3)	<.001	2071 (27.9)	3909 (30.4)	<.001
Previous conditions, No. (%)						
Cerebrovascular disease	917 (21.5)	1001 (26.9)	<.001	953 (12.8)	1808 (14.1)	.01
Chronic obstructive pulmonary disease	742 (17.4)	1175 (31.5)	<.001	419 (5.6)	1221 (9.5)	<.001
Myocardial infarction	2515 (59.0)	1725 (46.3)	<.001	3841 (51.8)	4520 (35.2)	<.001
Atrial fibrillation	1626 (38.2)	1422 (38.1)	.99			
CABG	947 (22.2)	539 (14.5)	<.001	1238 (16.7)	1240 (9.7)	<.001
PCI	1319 (31.0)	618 (16.6)	<.001	2927 (39.5)	1896 (14.8)	<.001
Medication use, No. (%)						
Statins	2719 (63.8)	1437 (38.5)	<.001	5307 (71.5)	5044 (39.2)	<.001
Calcium blockers	786 (18.4)	988 (26.5)	<.001	1964 (26.5)	3295 (25.6)	.19
ACE inhibitors	2816 (66.1)	1590 (42.7)	<.001	3268 (44.0)	3922 (30.5)	<.001

Certainly – for example we expect that patients with COPD will be at increased risk of MACE. Furthermore, patients with COPD are also less likely to receive β-blockade (for clinical reasons)

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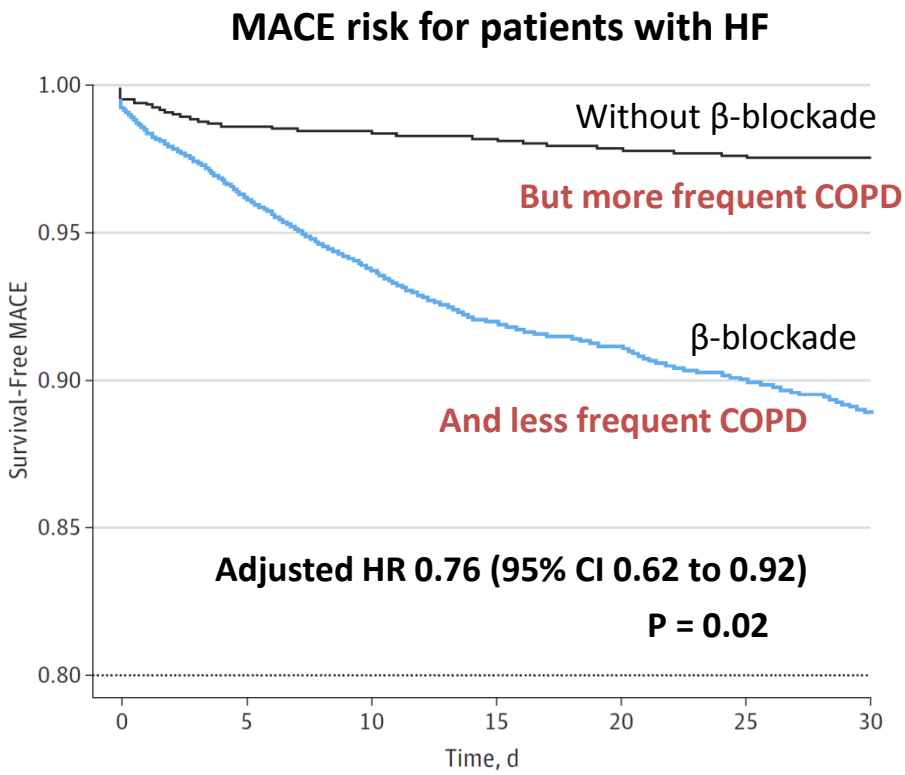
ACE inhibitors	2816 (66.1)	1590 (42.7)	<.001	3268 (44.0)	3922 (30.5)	<.001

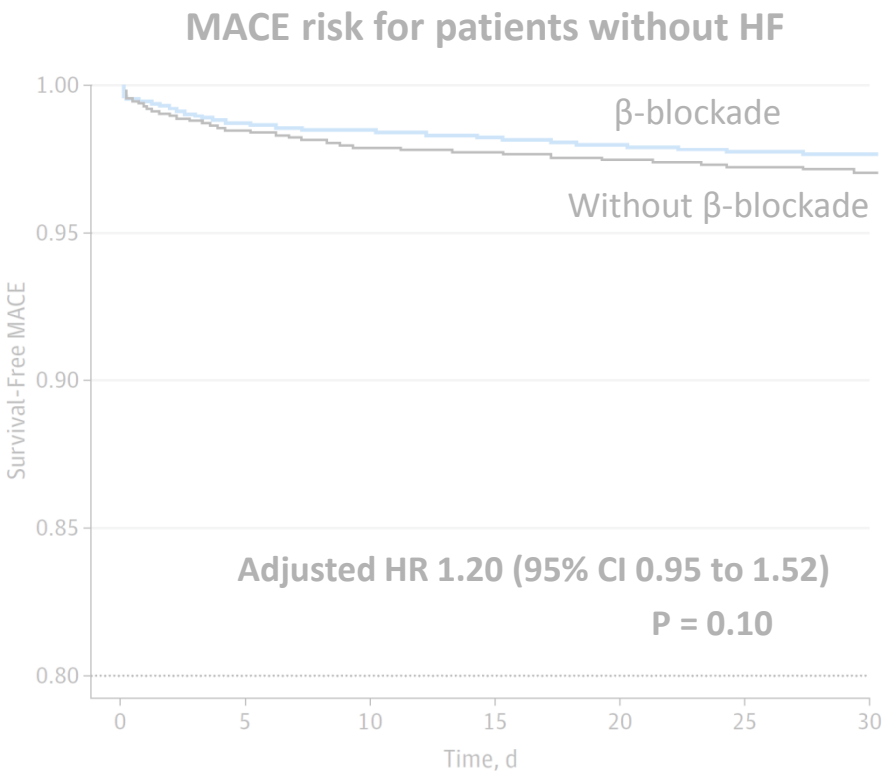
So we have a situation in which patients not receiving β-blockade are also more likely to have COPD. The difference between patients in the two β-blockade groups isn't just in their treatment, it's also in the likelihood that they have COPD.

Table 1. Baseline Characteristics

Characteristic	Heart Failure			No Heart Failure		
	β-Blockers (n = 4262)	No β-Blockers (n = 3728)	*P* Value for Difference	β-Blockers (n = 7419)	No β-Blockers (n = 12 854)	*P* Value for Difference
Age, mean (SD), y	73.4 (10.7)	76.1 (11.1)	<.001	68.8 (10.9)	68.8 (12.1)	.63
Male sex, No. (%)	2598 (61.0)	1981 (53.1)	<.001	4751 (64.0)	7505 (58.4)	<.001
Urgent surgery, No. (%)	1862 (43.7)	1912 (51.3)	<.001	2071 (27.9)	3909 (30.4)	<.001
Previous conditions, No. (%)						
Cerebrovascular disease	917 (21.5)	1001 (26.9)	<.001	953 (12.8)	1808 (14.1)	.01
Chronic obstructive pulmonary disease	742 (17.4)	1175 (31.5)	<.001	419 (5.6)	1221 (9.5)	<.001
Myocardial infarction	2515 (59.0)	1725 (46.3)	<.001	3841 (51.8)	4520 (35.2)	<.001
Atrial fibrillation	1626 (38.2)	1422 (38.1)	.99			
CABG	947 (22.2)	539 (14.5)	<.001	1238 (16.7)	1240 (9.7)	<.001
PCI	1319 (31.0)	618 (16.6)	<.001	2927 (39.5)	1896 (14.8)	<.001
Medication use, No. (%)						
Statins	2719 (63.8)	1437 (38.5)	<.001	5307 (71.5)	5044 (39.2)	<.001
Calcium blockers	786 (18.4)	988 (26.5)	<.001	1964 (26.5)	3295 (25.6)	.19
ACE inhibitors	2816 (66.1)	1590 (42.7)	<.001	3268 (44.0)	3922 (30.5)	<.001

Which raises the question – is the adverse outcome observed among HF patients who don't receive β-blockade more a function of the absence β-blockade or the presence of COPD? That is, is the effect of β-blockade *confounded* by COPD?





Potential *confounders* are factors which are associated with *both* the risk factor of interest *and* the outcome. In this situation the risk factor of interest may be a victim of "guilt by association" – it may simply be serving as an innocent *marker* for some other "true cause".

Table 1. Baseline Characteristics

Characteristic	Heart Failure			No Heart Failure		
	β-Blockers (n = 4262)	No β-Blockers (n = 3728)	*P* Value for Difference	β-Blockers (n = 7419)	No β-Blockers (n = 12 854)	*P* Value for Difference
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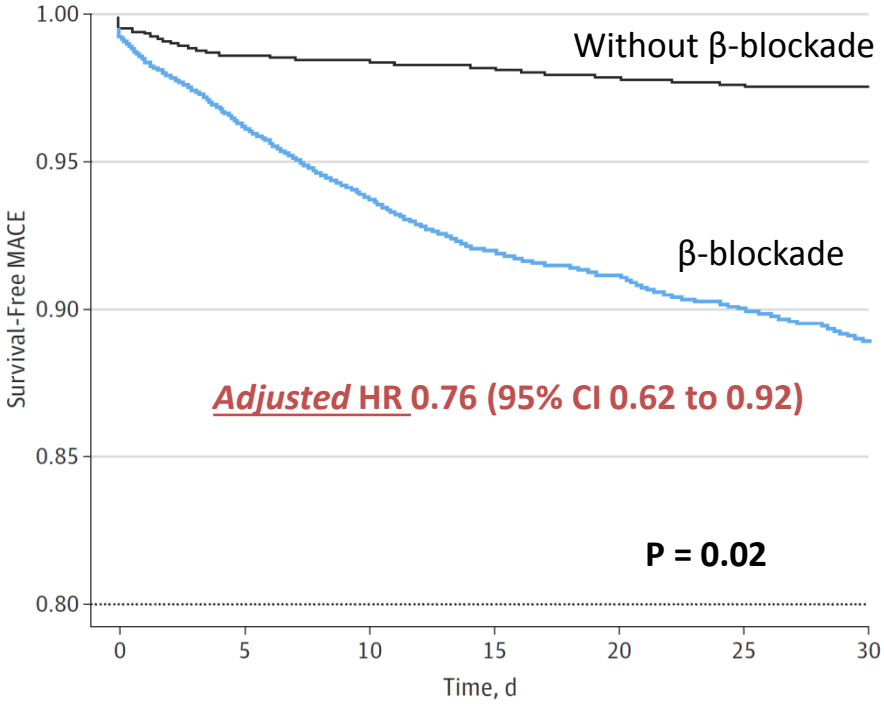
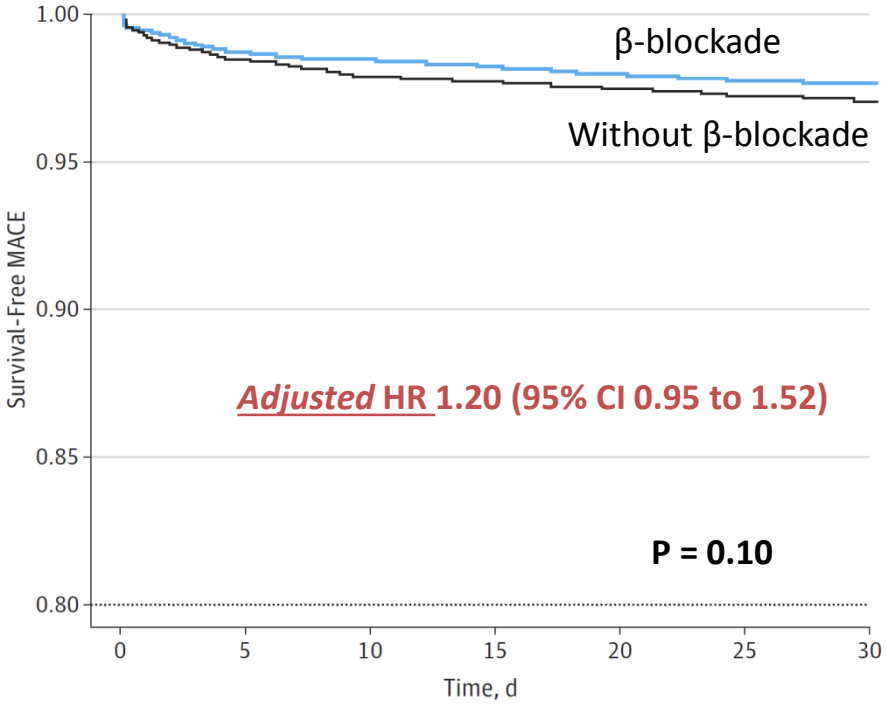
An appropriate analysis will *control* for potential confounders and yield an *adjusted estimate* of a factor's effect size. Note, however, that any imbalance created by non-randomized assignment of treatment can never be undone, only statistically addressed.

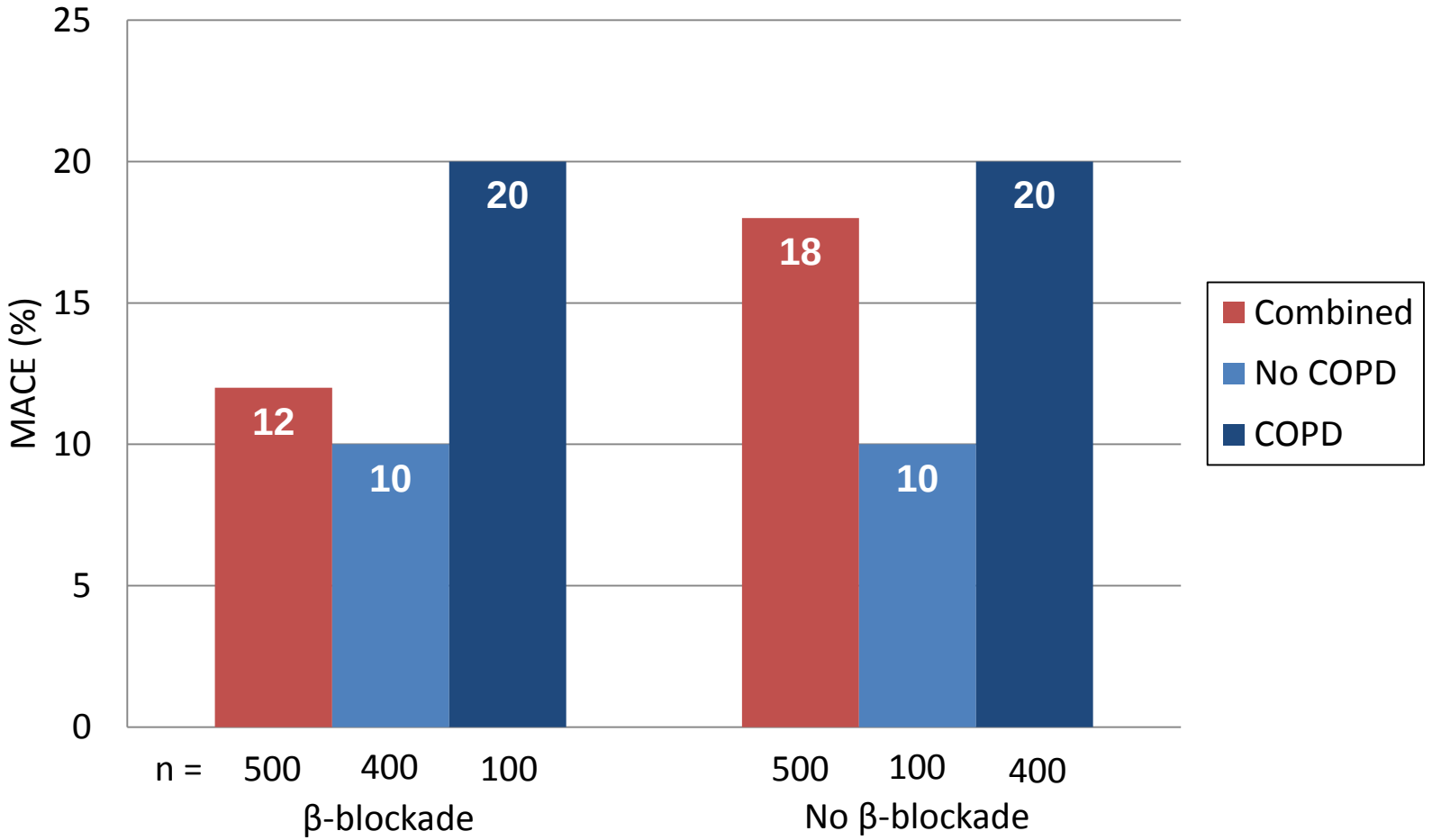
MACE risk for patients with HF



MACE risk for patients without HF

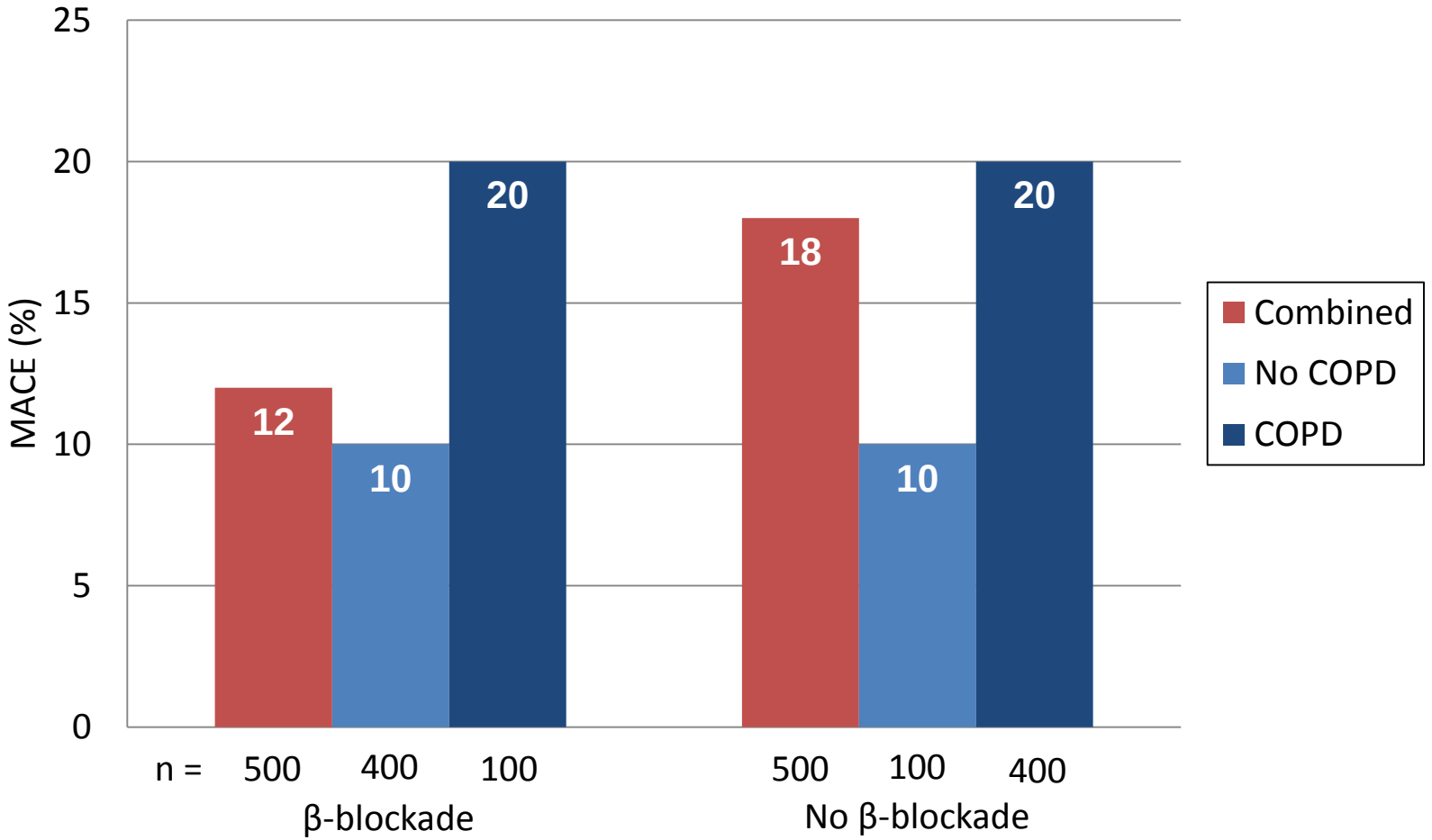


Just as we did for effect modification, let's examine confounding. Imagine that the authors had presented this (hypothetical) data examining the relationships among perioperative β-blockade, COPD and adverse cardiovascular outcomes (MACE)

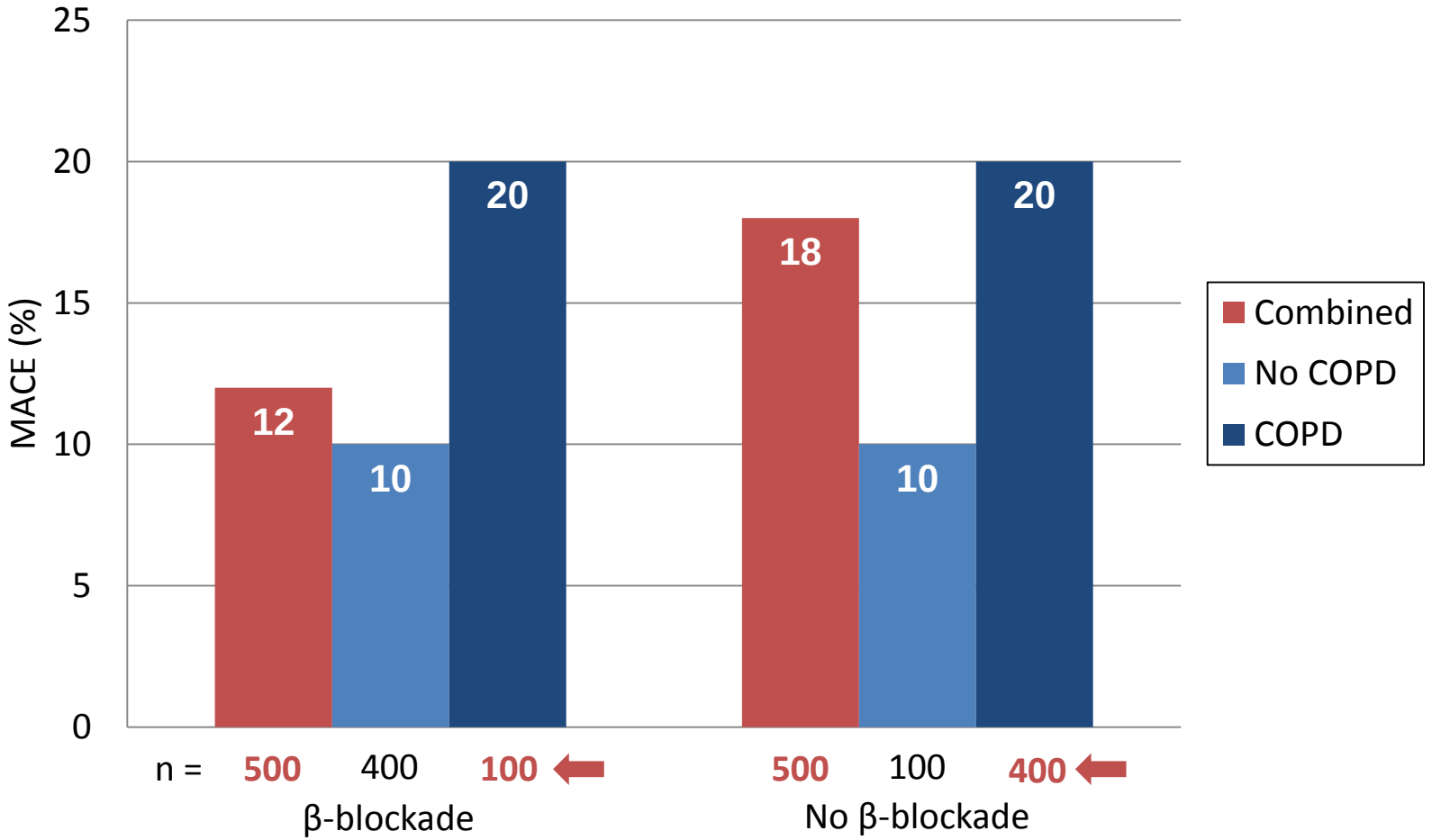


The questions we'll be considering

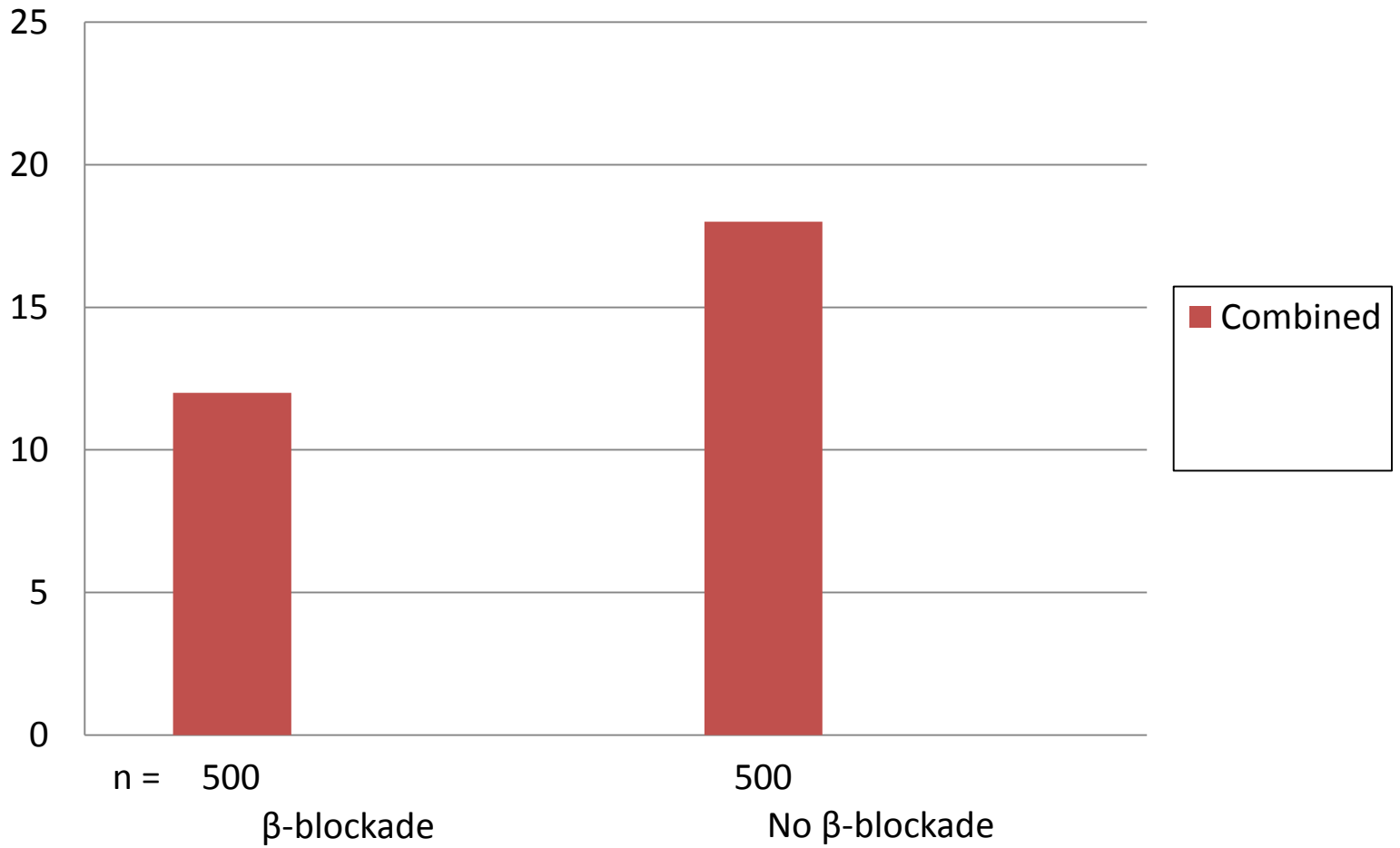
1. Is there an "overall" association between β-blockade and MACE?
2. How strong is the association for patients with vs without COPD?
3. What do you conclude?



500 of the study patients have COPD while 500 do not. However, COPD is not equally distributed across the treatment groups and is much less common among patients who receive β-blockade (100 of 500) than among those who don't (400 of 500).

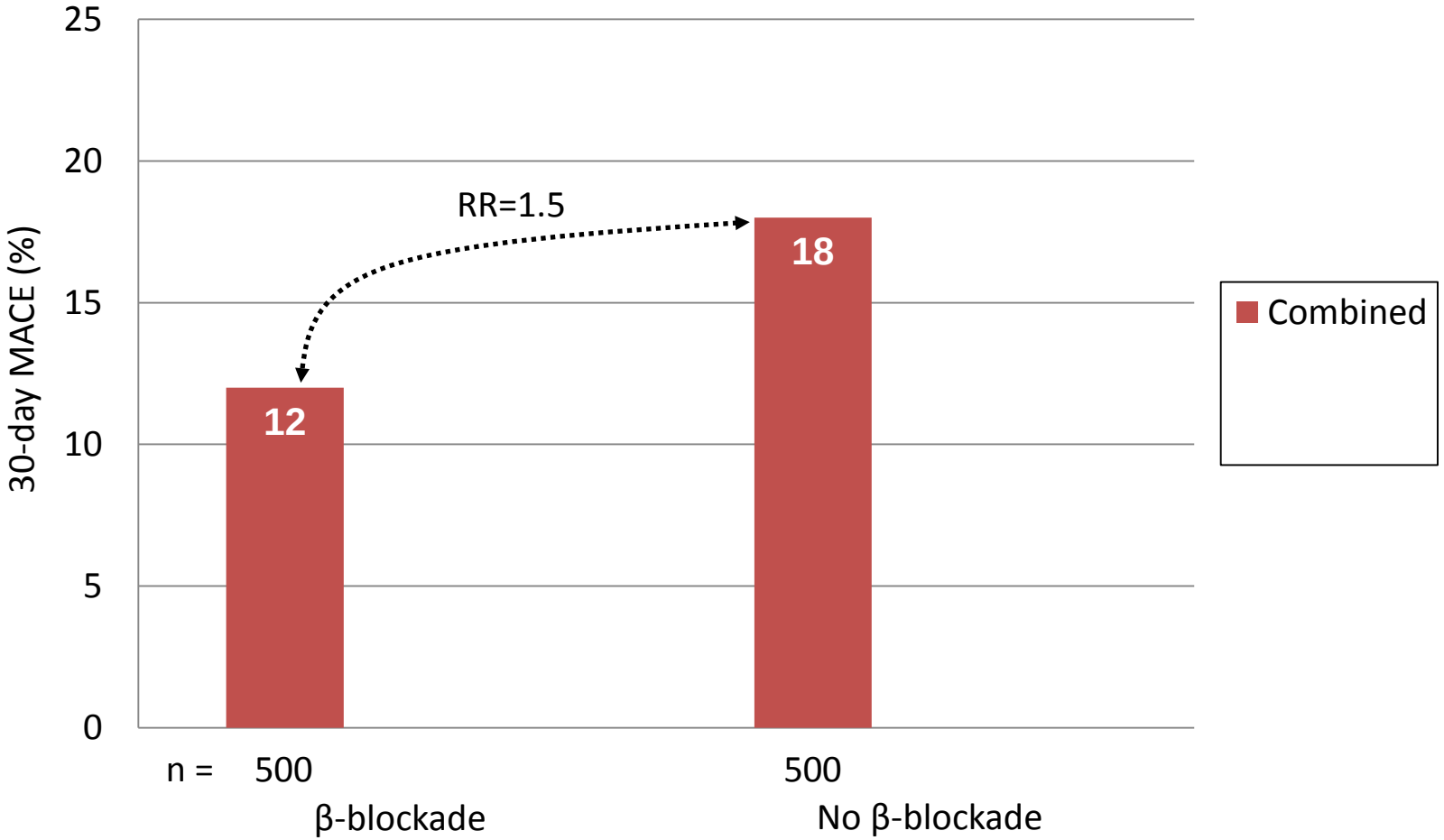


Question 1: Is the omission of β-blockade a risk factor for MACE?

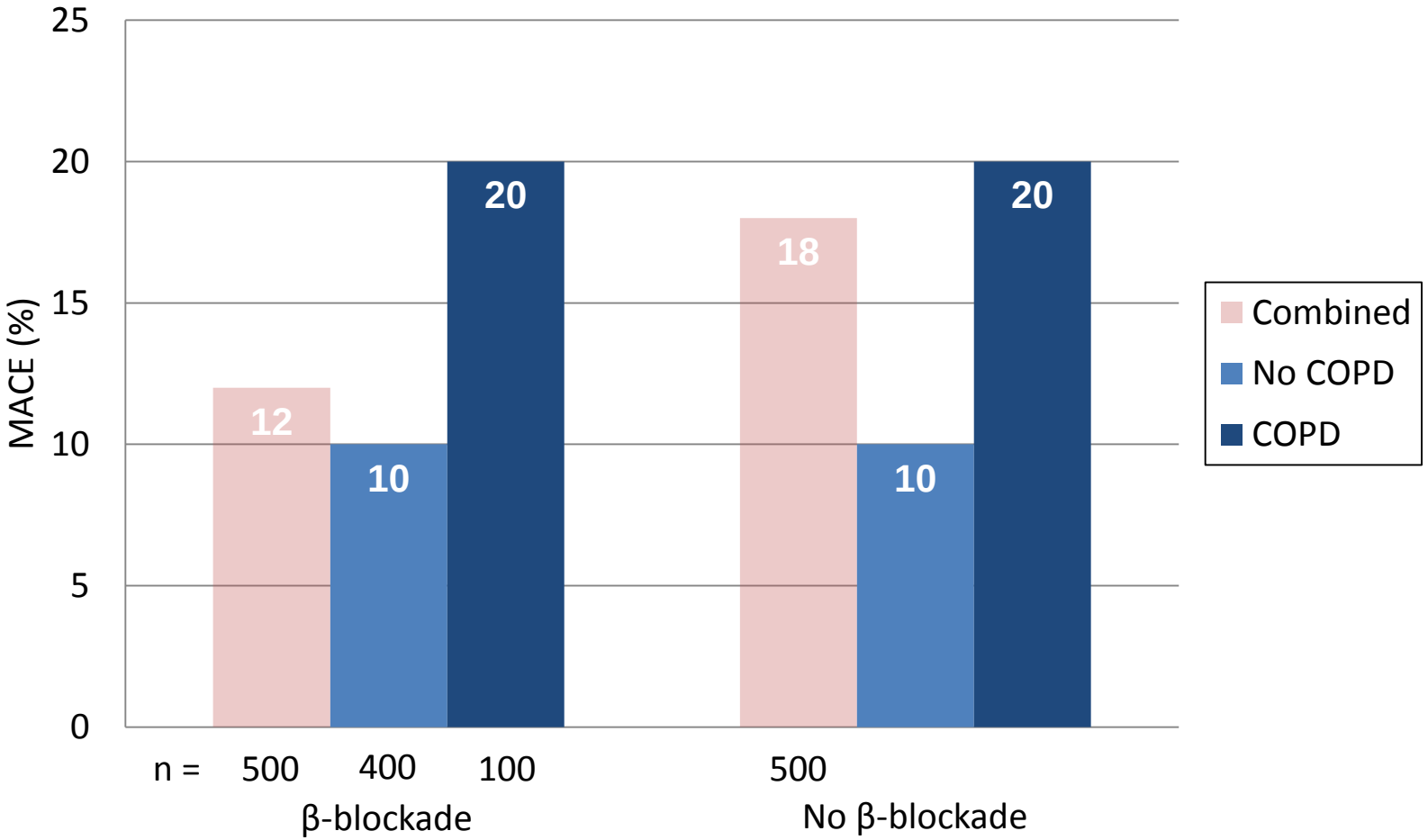


Question 1: Is the omission of β-blockade a risk factor for MACE?

Apparently so – the risk of an adverse event is 12% if β-blockade is provided but 18% if it's omitted. Risk increases by 50% (RR=1.5)



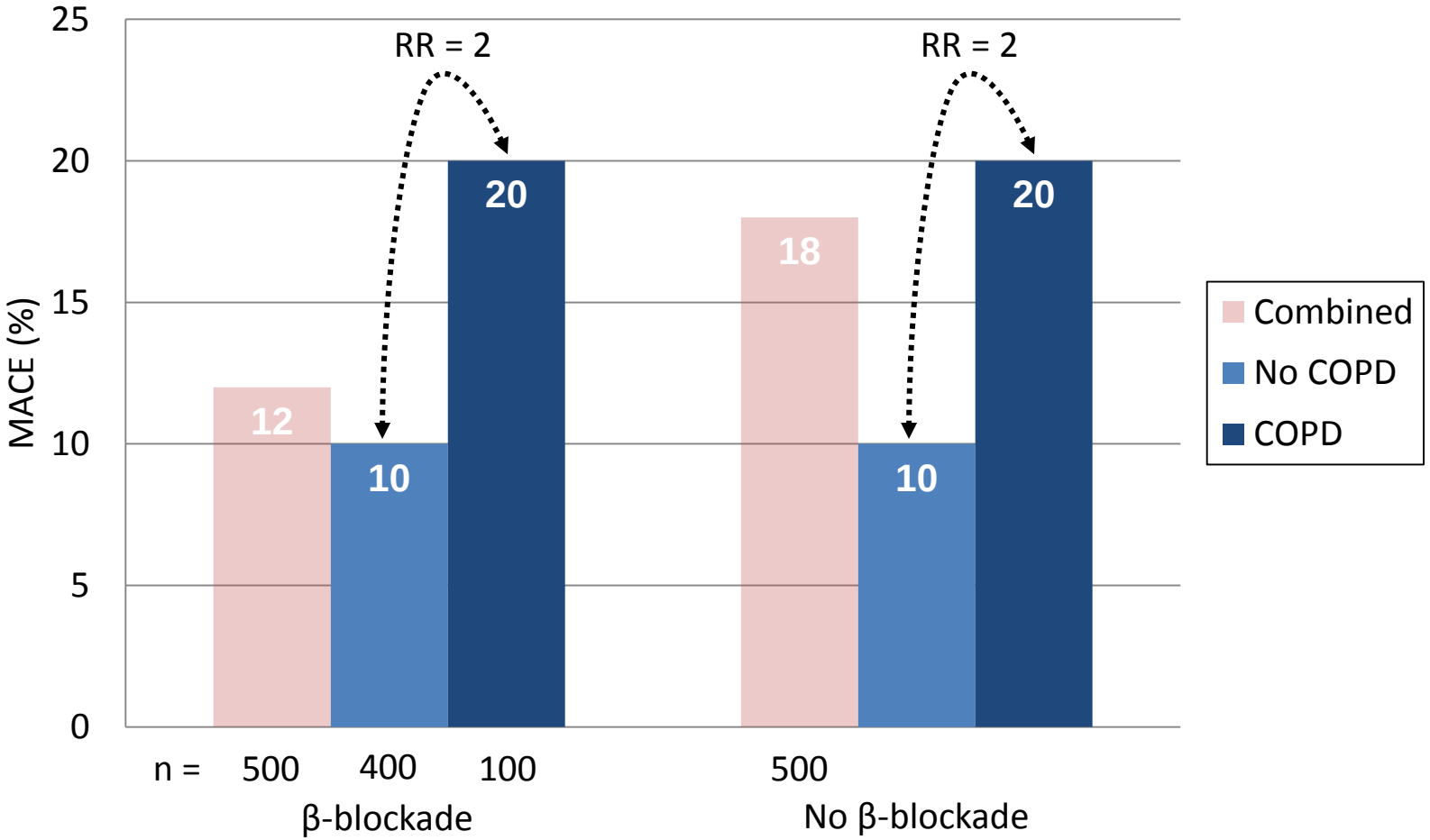
Next consider the impact of COPD – does COPD influence risk?



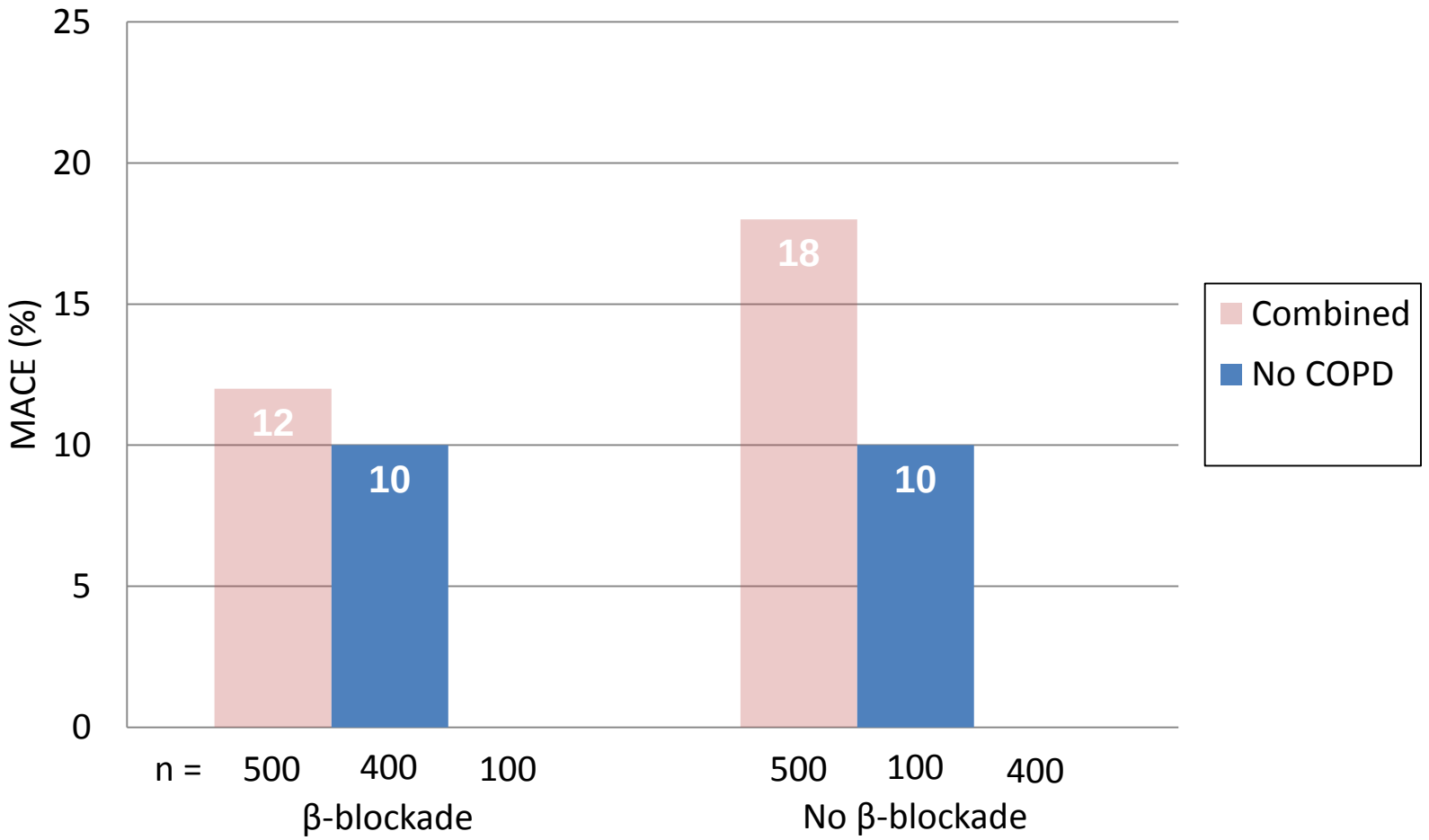
EBM journal club (R. Burack, 2014)

Next consider the impact of COPD – does COPD influence risk?

Again the answer appears to be yes – patients with COPD face double the risk of an adverse event whether they receive β-blockade or not (20% vs 10%, RR = 2 in both groups)



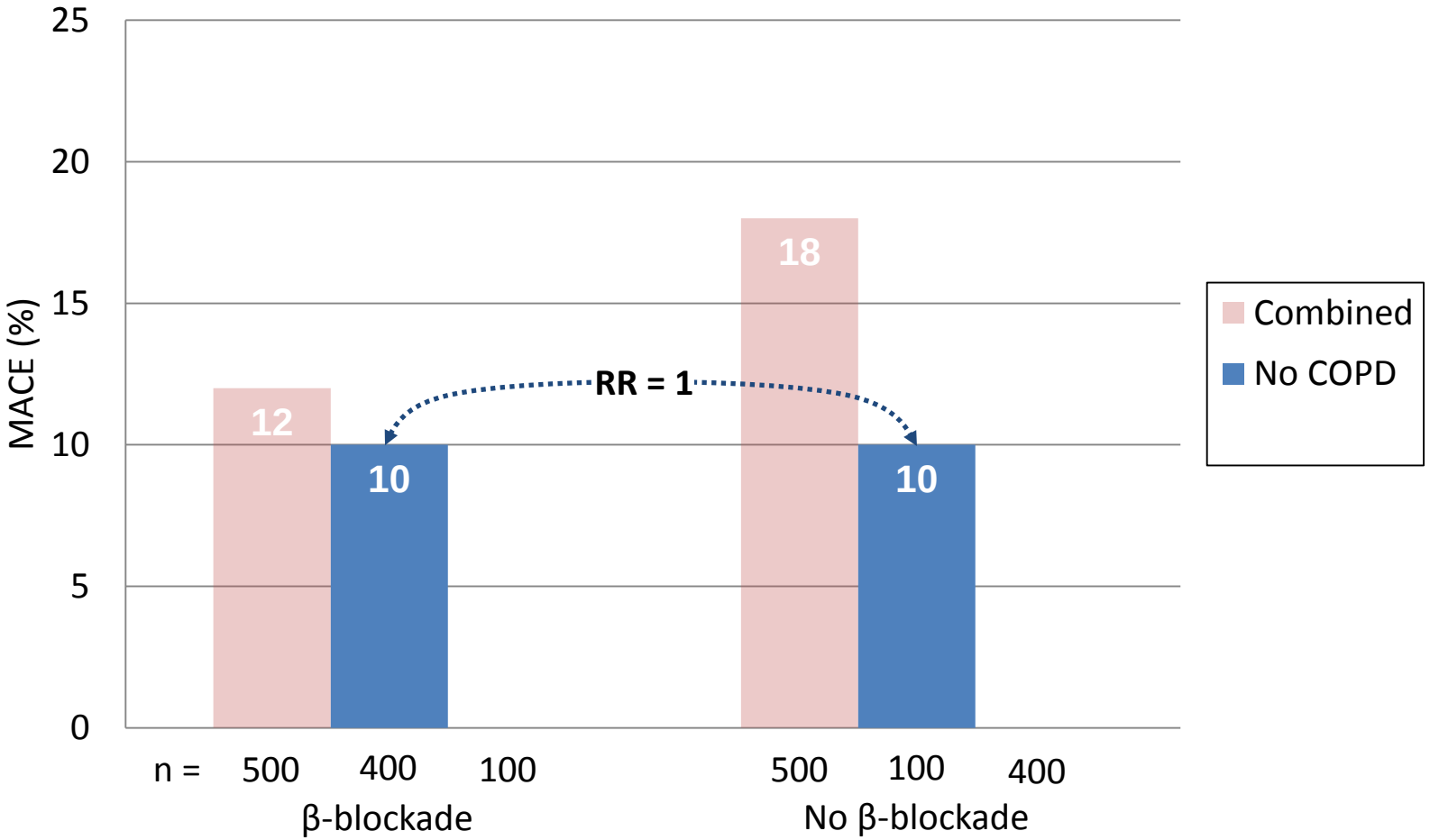
Now let's ask the β-blockade question according to COPD status – for patients *without* COPD what is the risk of omitting β-blockade?



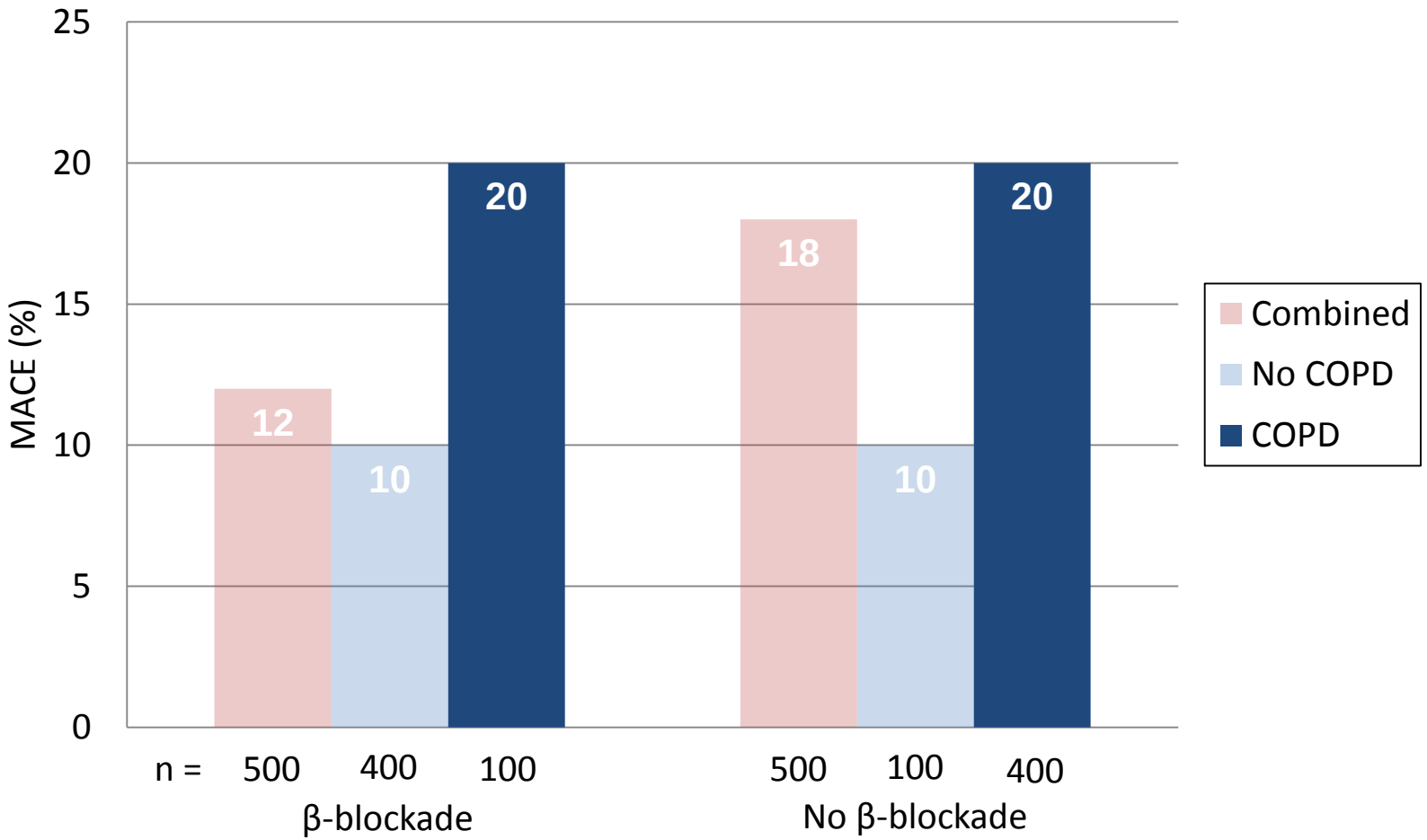
EBM journal club (R. Burack, 2014)

Now let's ask the β-blockade question according to COPD status – for patients *without* COPD what is the risk of omitting β-blockade?

There is no effect – among COPD-free patients MACE risk is 10% if they receive β-blockade and the *same 10%* if they don't (RR=1)



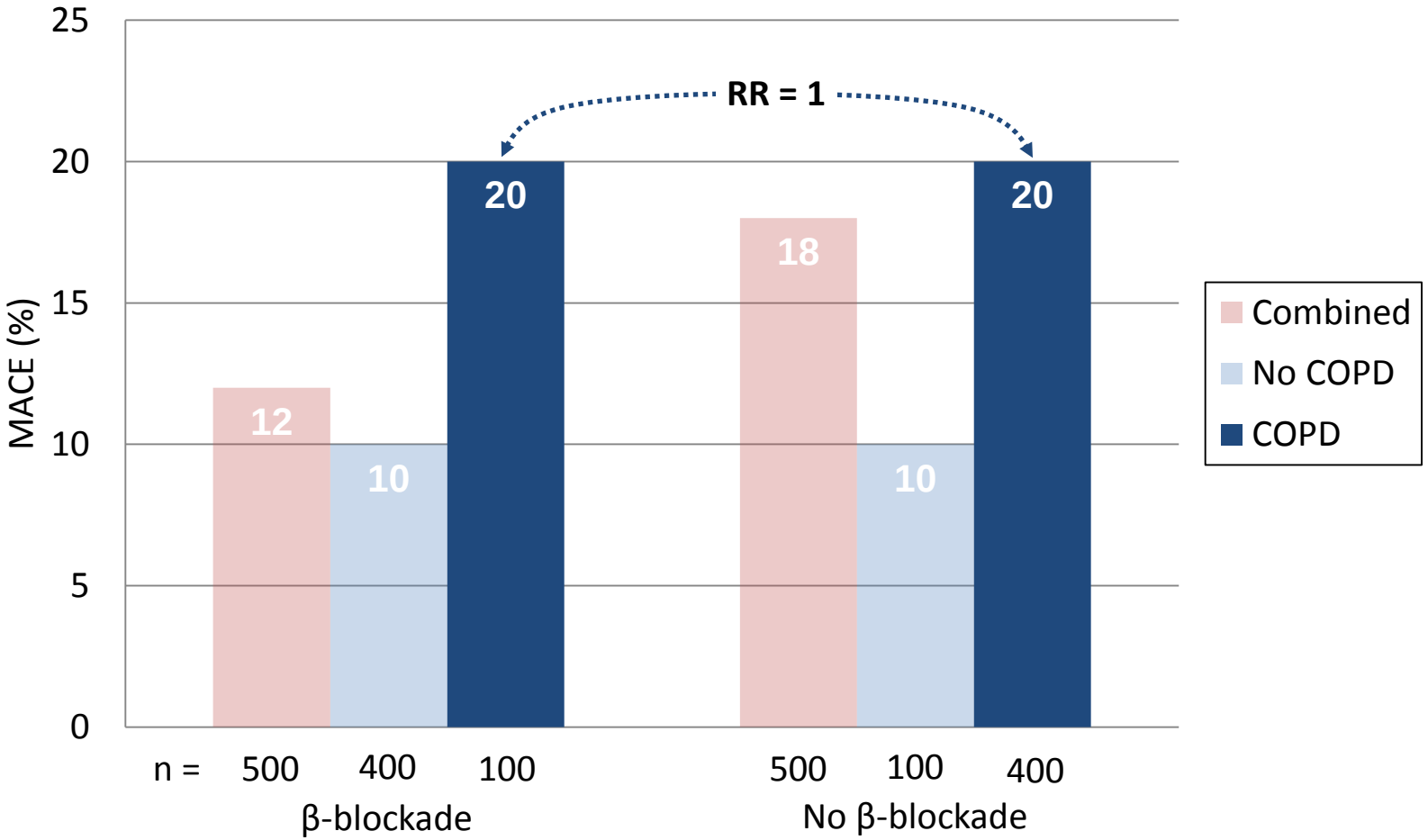
So that's interesting, but what about for patients *with* COPD?



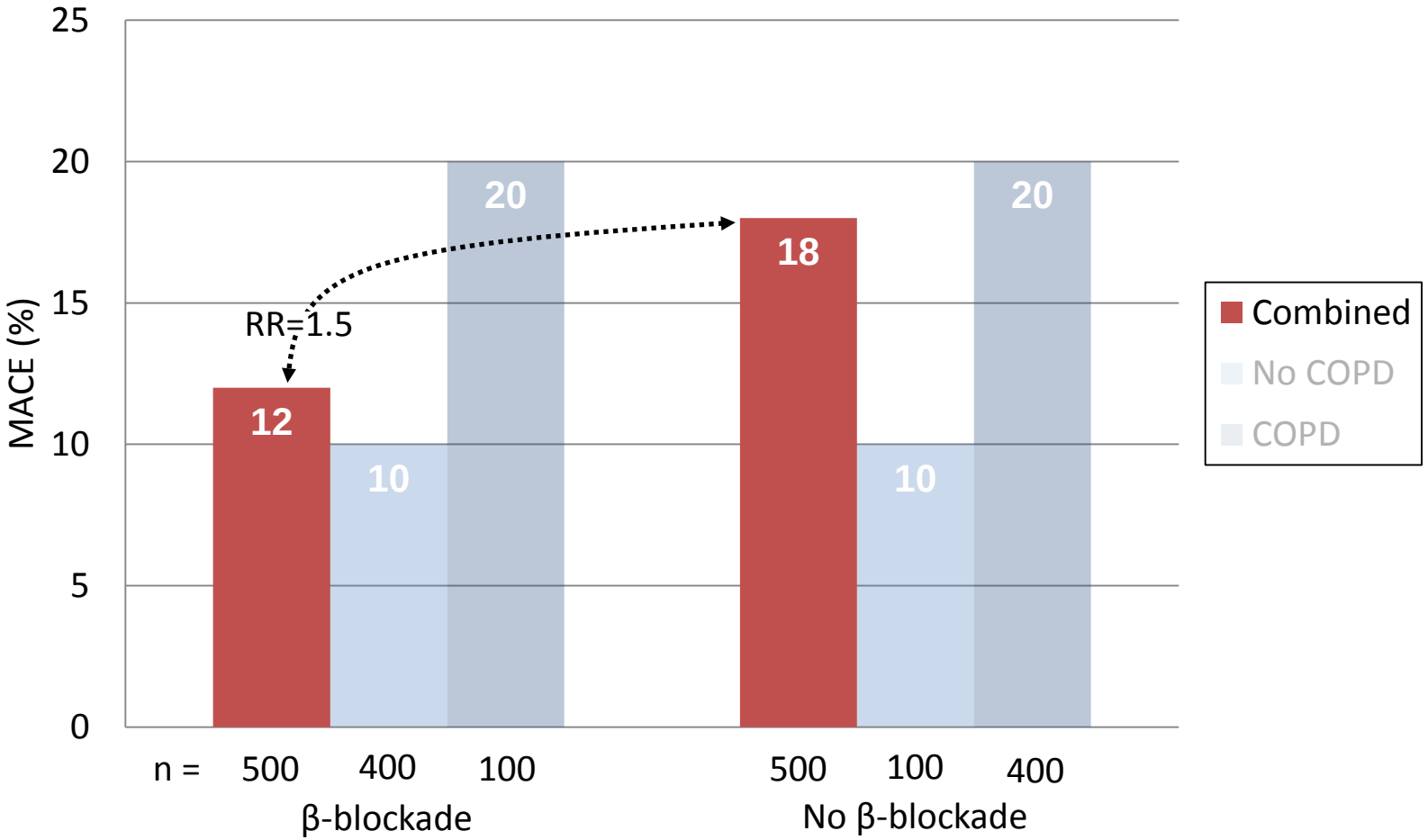
EBM journal club (R. Burack, 2014)

So that's interesting, but what about for patients *with* COPD?

We observe the same pattern – while the risk of MACE is higher if the patient has COPD, the absolute level of risk among patients with COPD is the same 20% whether β-blockade is omitted or not (RR = 1).

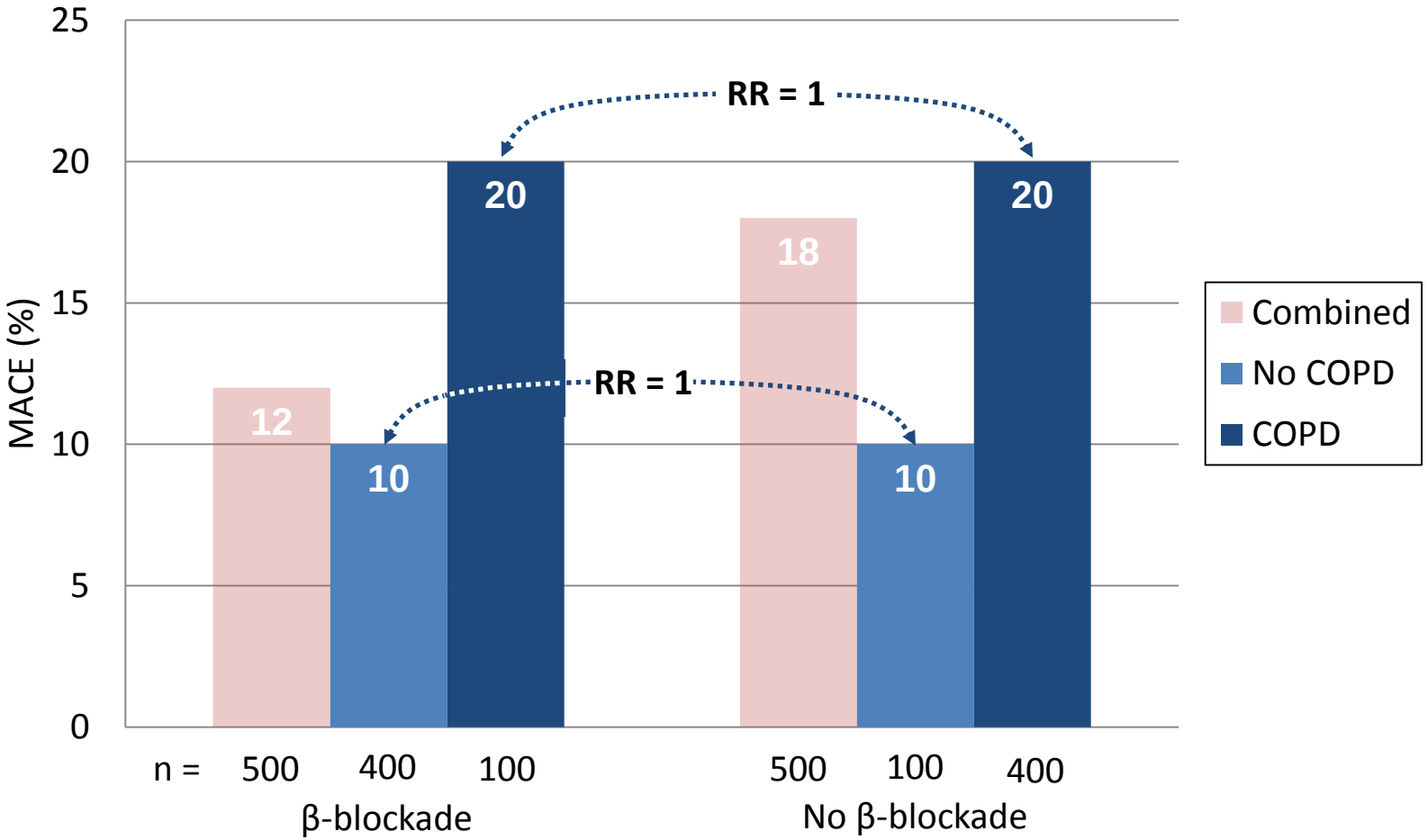


So now we have an even more interesting situation.
From the perspective of the population as a whole it appears that the omission of β-blockade is associated with a 50% increase in risk.

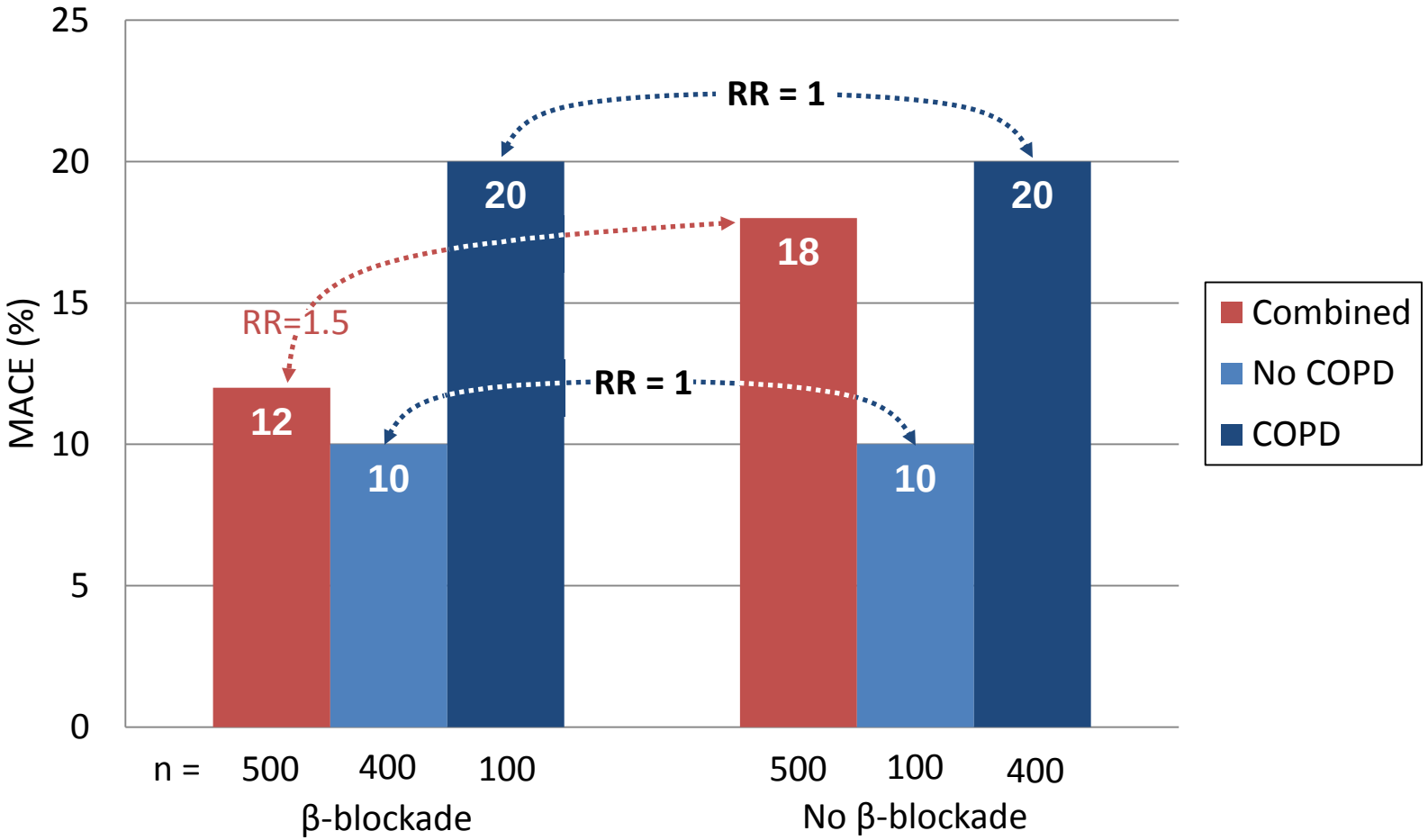


EBM journal club (R. Burack, 2014)

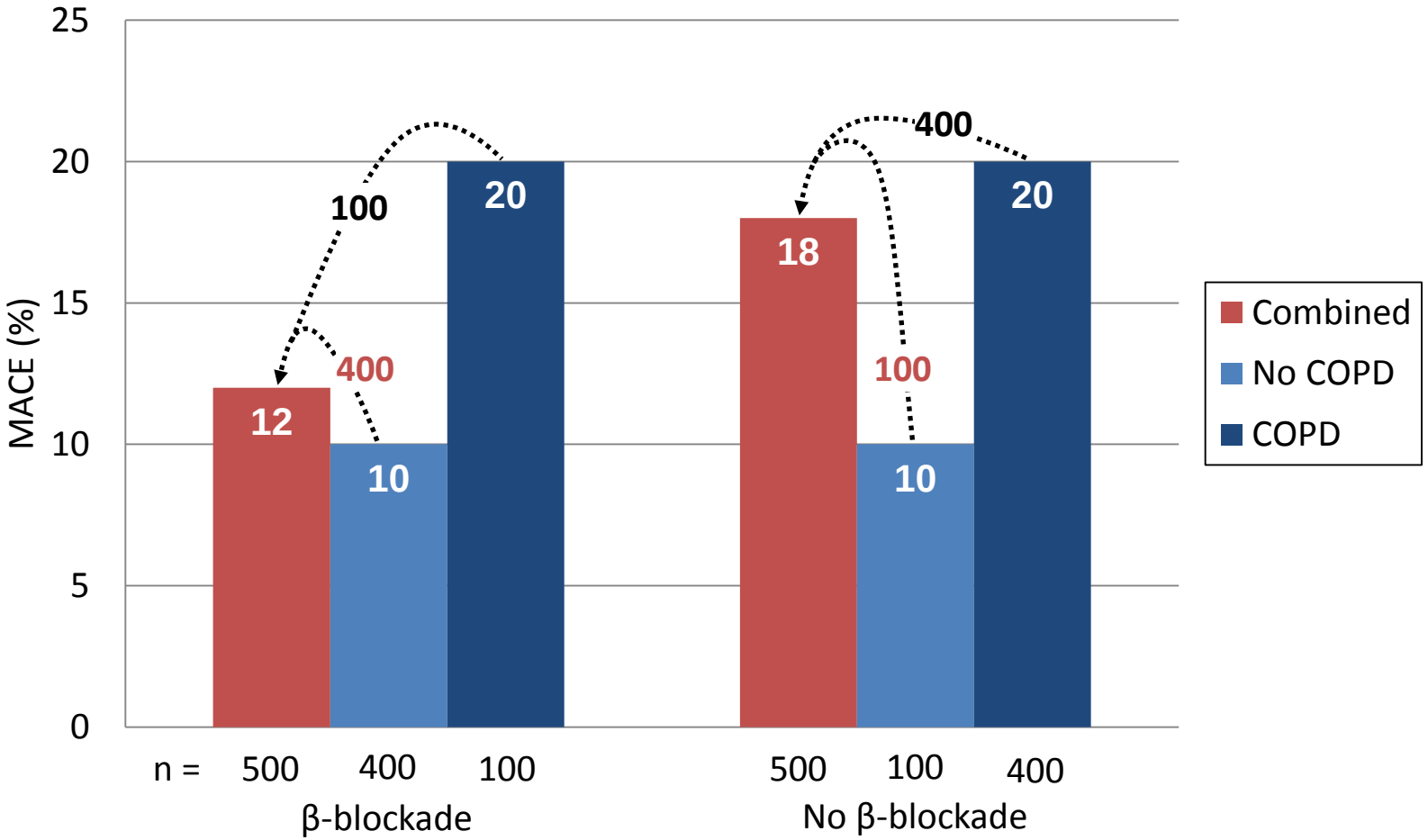
Yet among patients either with or without COPD we see no evidence a β-blockade effect (RR = 1 in each case).



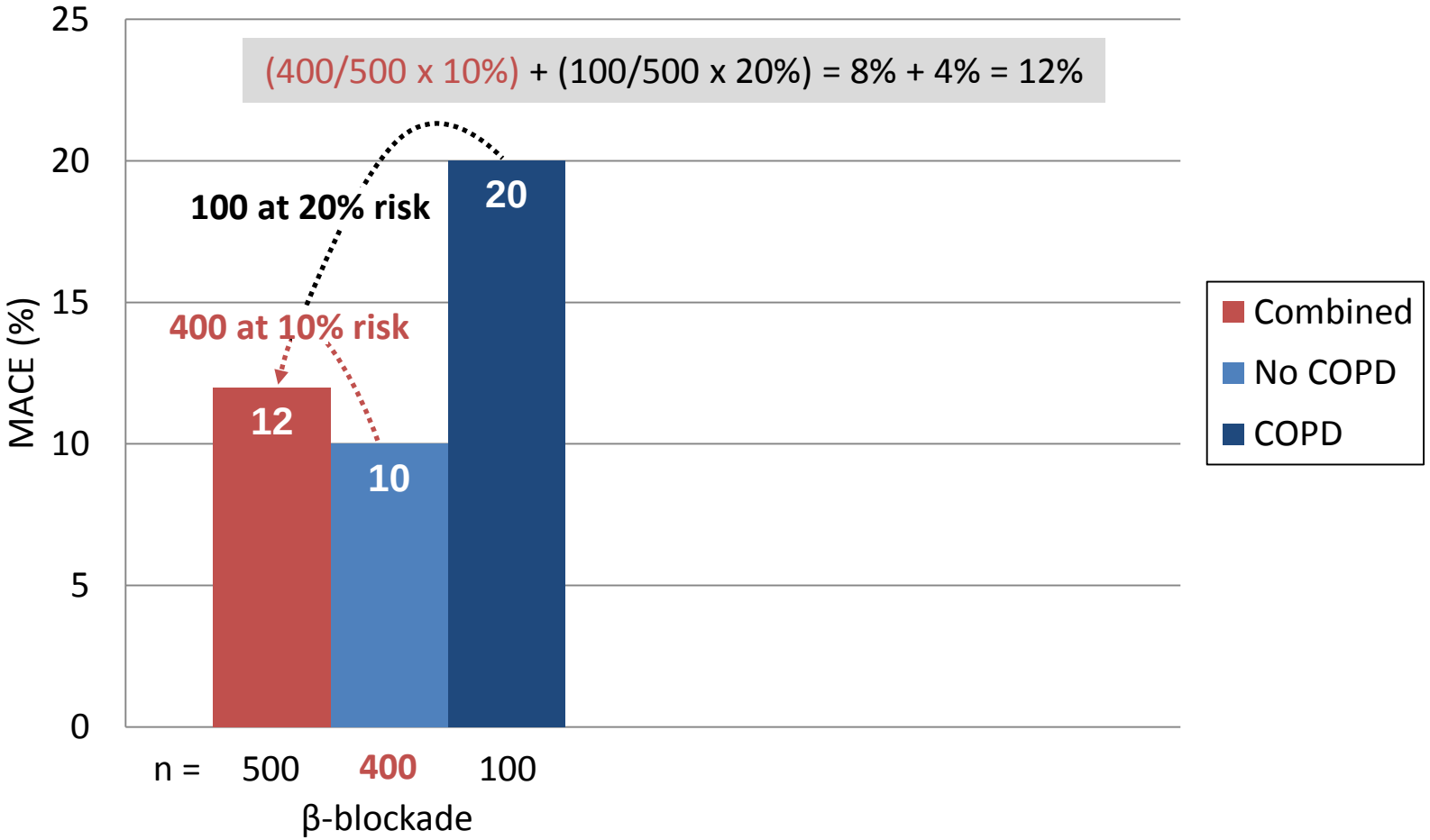
So how do we explain this apparent paradox – the omission of β-blockade increases MACE risk 50% in the population as a whole but not at all when examined separately in the two COPD subgroups who together comprise the entire study population?



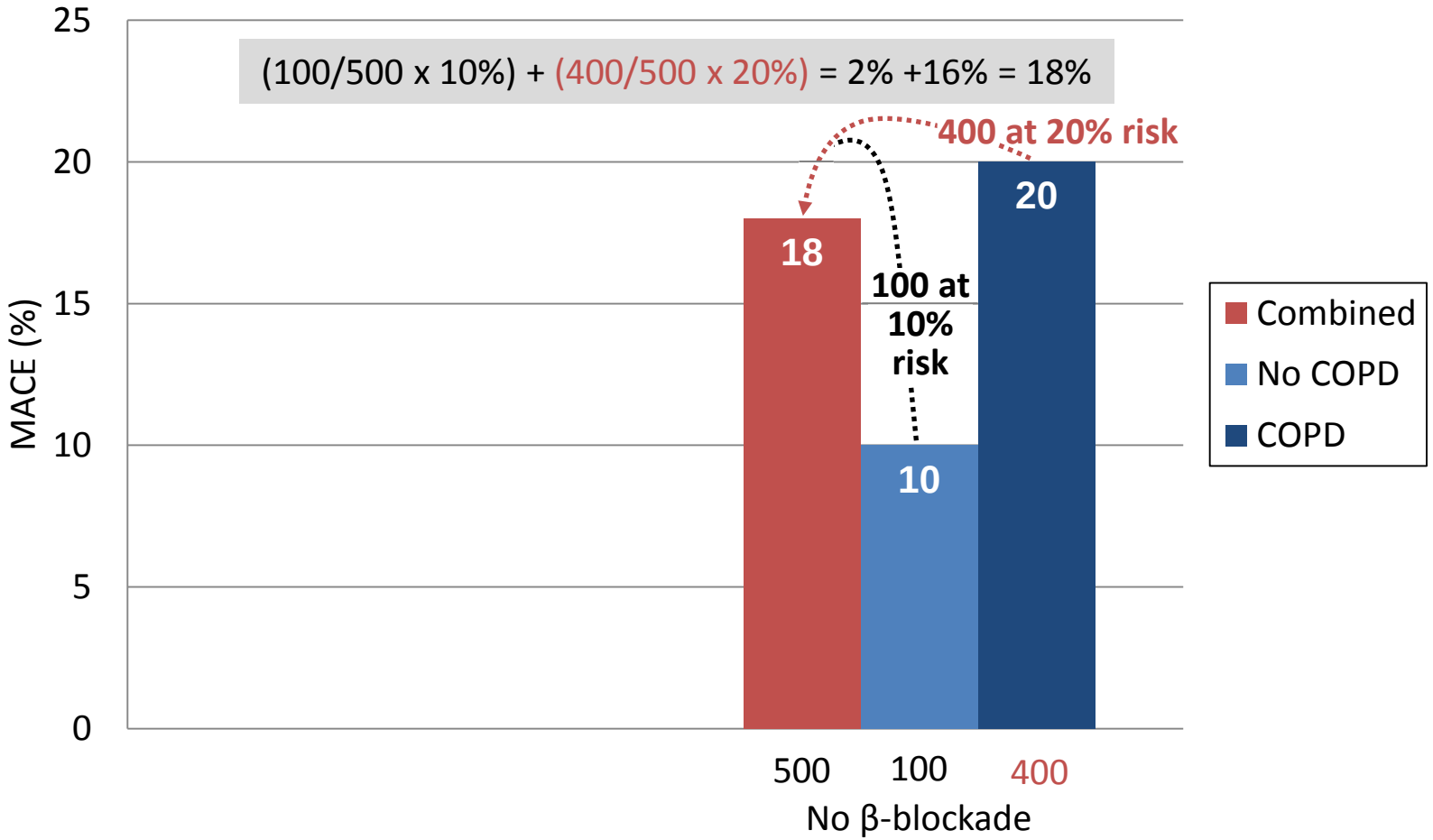
Blame it on mathematics, weighted averages and confounding. The “overall” effect we observe in the β-blockade groups is simply a weighted average of what we see in their member COPD subgroups



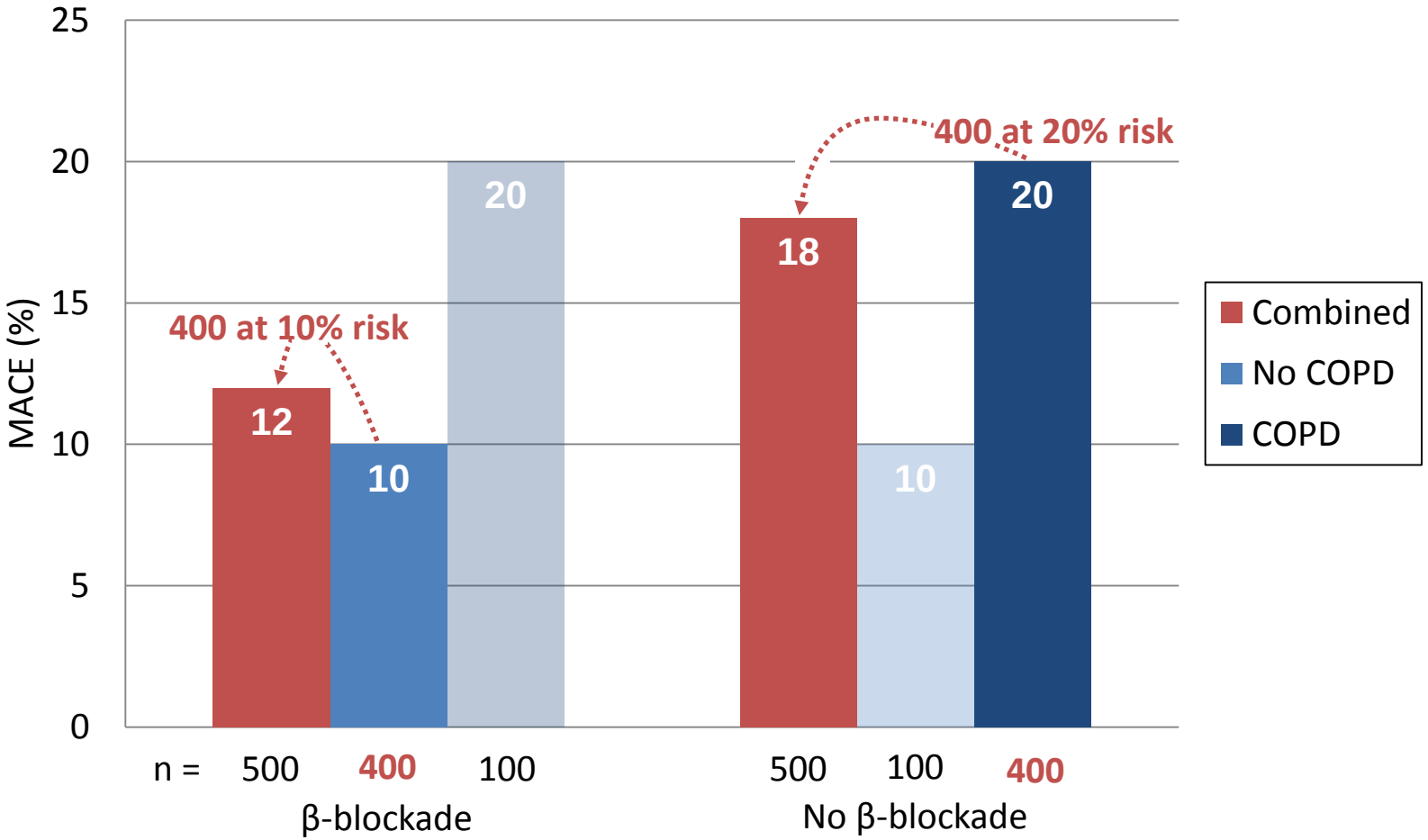
The overall risk of 12% observed among the 500 patients who receive β-blockade is dominated by the experience of the 400 patients who *don't have* COPD (and whose risk is only 10%).



On the other hand, the overall risk level among patients who don't receive β-blockade is much higher (18%) since this group is dominated by the 400 patients who *do have* COPD (risk 20%).



It's weighted averaging that underlies confounding. The apparent association between β-blockade omission and MACE is an artifact of the unequal distribution of COPD between the blockade groups. β-blockade omission serves as a *marker*, not determinant, of high risk.

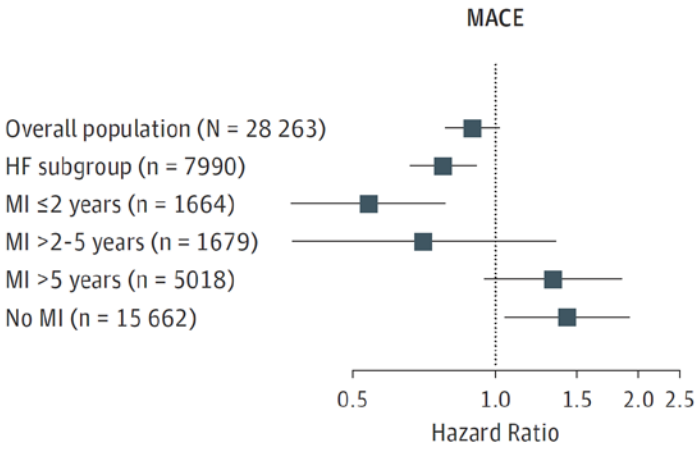


Back to our patient

- Mr. Jones is a 68 year old man who presents for pre-operative evaluation in advance of elective hip replacement surgery
- His past medical history includes stable angina, hypertension and hyperlipidemia (all well-controlled) without previous MI or revascularization), CHF, vascular disease, diabetes or smoking.
- His physical exam reveals BP of 126/78 with no evidence of cardiovascular disease (and is otherwise unremarkable)
- His current medications include ACE inhibitor, statin, aspirin
- Do you recommend perioperative beta-blockade?
  - ❑ *Yes - it carries a Class IIa AHA guideline recommendation*
  - ❑ *Yes - he has documented angina and 2 risk factors*
  - ❑ *No – it's unnecessary and potentially harmful*
  - ❑ *Let's consult cardiology*

No, since there's no evidence it will reduce his risk.
Taking HF, previous MI and all other *measured* risk factors into account, the benefit of perioperative β-blockade is limited to those patients who had a strong pre-operative indication for β-blockade (and among whom we'd be ill-advised to discontinue it)

Figure 1. Hazard Ratios Associated With β-Blockers in Different Subgroups



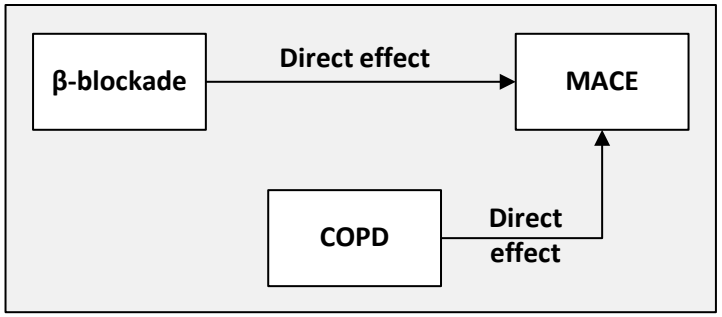
The effects associated with β-blockers differed in patients with and without heart failure (HF) ($P < .001$ for interactions between β-blockers and HF for both end points). Among the subgroup without HF, the hazard ratios associated with β-blockers were further dependent on a history of MI and time elapsed since the most recent MI (for interaction between β-blockers and MI categories, $P < .001$ for MACE and $P = .02$ for all-cause mortality). Analysis was adjusted for all variables from Table 1 plus calendar year for surgery. MACE indicates major adverse cardiovascular events (nonfatal ischemic stroke, acute myocardial infarction, and cardiovascular death); MI, myocardial infarction.

Effect modification

Adjustment for confounding

Supplemental material

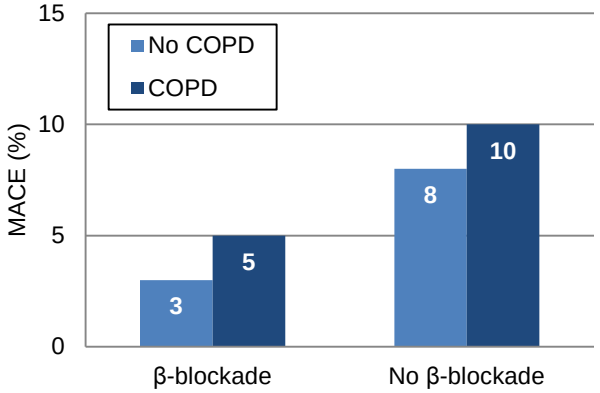
Confounding and effect modification are alternatives to a simple *additive model*



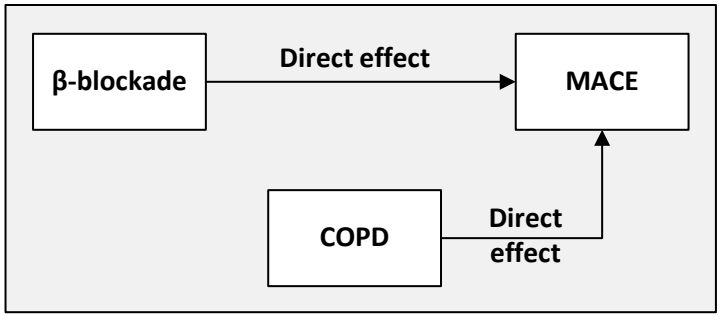
Additive model

$$p(MACE) = a + b_1(\beta) + b_2(COPD)$$

(effect of one factor simply adds to the effect of the other)



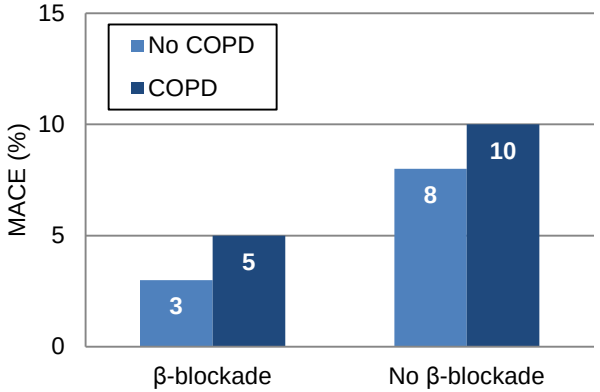
With effect modification the two factors no longer simply add together – their effects "multiply" if both are present simultaneously

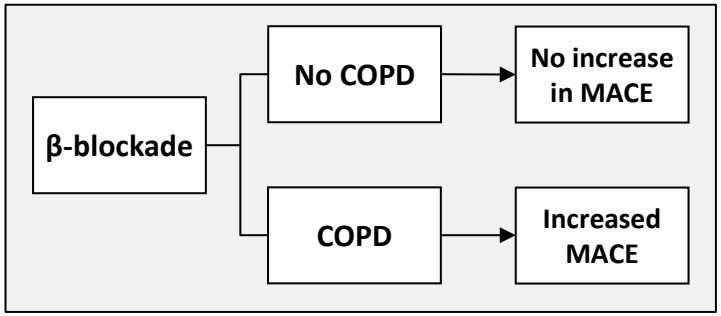


Additive model

$p(MACE) = a + b_1(\beta) + b_2(COPD)$

(effect of one factor simply adds to the effect of the other)

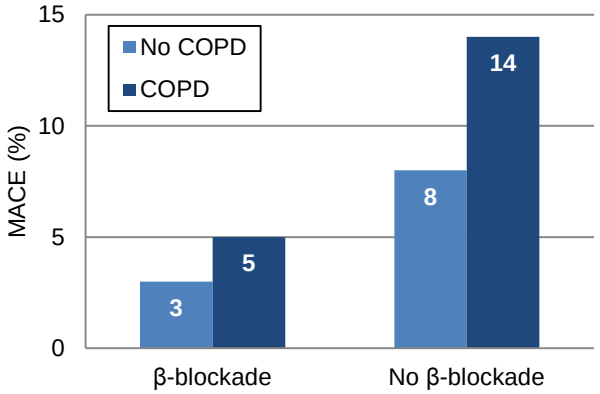




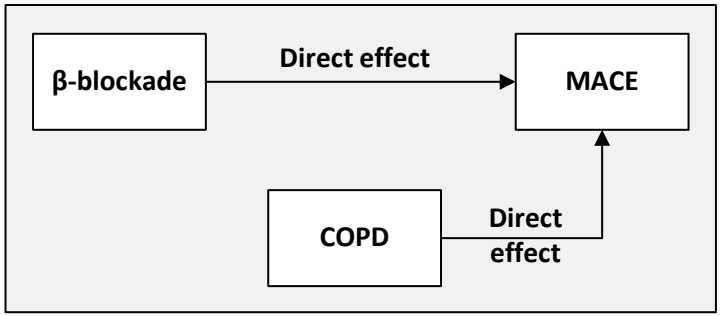
Effect modification

$p = a + b_1(\beta) + b_2(COPD) + b_3(\beta * COPD)$

(effect of one factor depends on the status of the other)



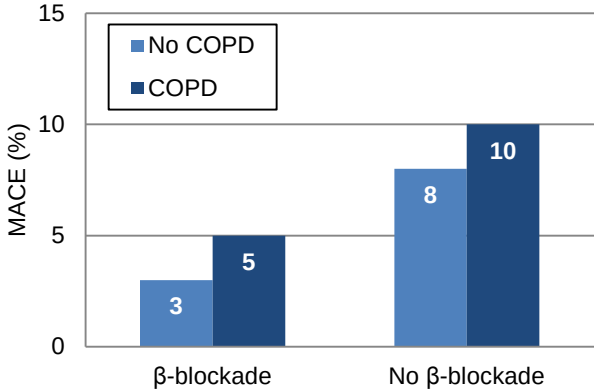
With confounding the effect of one factor may be partially or fully explained by its serving as a *marker* for another (coefficients change from additive model)

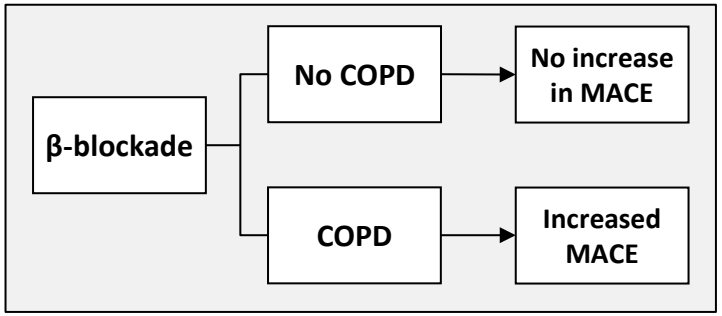


Additive model

$p(MACE) = a + b_1(\beta) + b_2(COPD)$

(effect of one factor simply adds to the effect of the other)

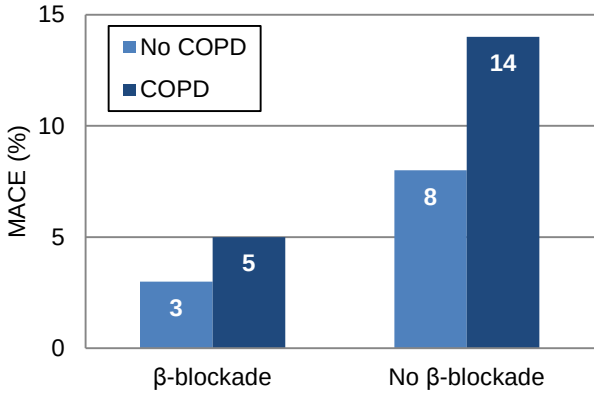


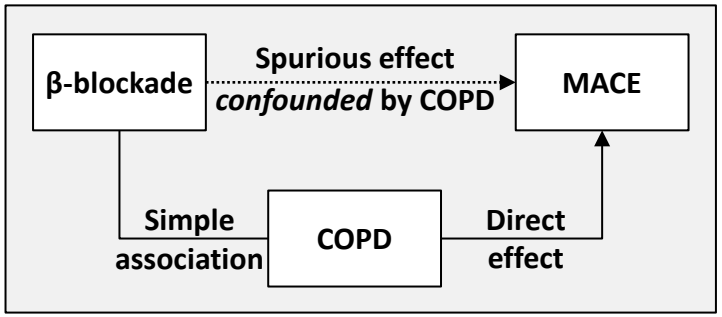


Effect modification

$p = a + b_1(\beta) + b_2(COPD) + b_3(\beta * COPD)$

(effect of one factor depends on the status of the other)

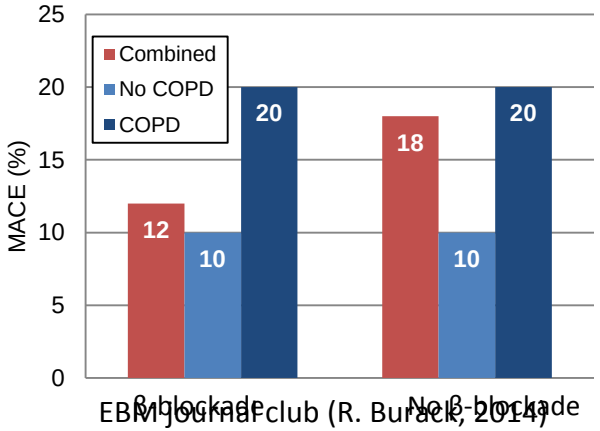




Confounding

$p(MACE) = a + b_4(\beta) + b_5(COPD)$

(the apparent effect of one factor is attributable to its serving as a *marker* for another "causal" factor)



Caution

The following slides are filled with numbers and intended only for readers who tolerate such things.

But if you require a mathematical demonstration of confounding before you can accept its existence just “fill in the blanks” and see if you’re convinced.

Let's examine the effect of β-blockade among patients with or without COPD.
First what's the effect (RR) of β-blockade among those without COPD?

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	**Yes**	40	10	
	No	360	90	
	Total	400	100	500
	Risk	?	?	

RR = ?

Let's examine the effect of β-blockade among patients with or without COPD.
First what's the effect (RR) of β-blockade among those without COPD?

Simple enough – β-blockade has no effect – risk is 10% in both groups (RR = 1)

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	**Yes**	**40**	**10**	
	No	**360**	**90**	
	Total	**400**	**100**	500
	Risk	**10%**	**10%**	

RR = 1.0

And what's the β-blockade effect among patients who do have COPD?

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500
	Risk	10%	10%	

RR = 1.0

With COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	20	80	
	No	80	320	
	Total	100	400	500
	Risk	?	?	

RR = ?

And what's the β-blockade effect among patients who do have COPD?

While MACE risk is higher among patients with compared to without COPD (20% vs 10%), β-blockade adds nothing more to their increased risk (RR=1).

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500
	Risk	10%	10%	

RR = 1.0

With COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	20	80	
	No	80	320	
	Total	100	400	500
	Risk	20%	20%	

RR = 1.0

So now let's combine the results. Adding together the 500 patients who have COPD and the 500 who do not we arrive at a total study population of 1,000.

Without COPD

		β-blockade: Yes	β-blockade: No
MACE	**Yes**	40	10
	No	360	90
	Total	400	100
	Risk	10%	10%

500

With COPD

		β-blockade: Yes	β-blockade: No
MACE	**Yes**	20	80
	No	80	320
	Total	100	400
	Risk	20%	2%

500

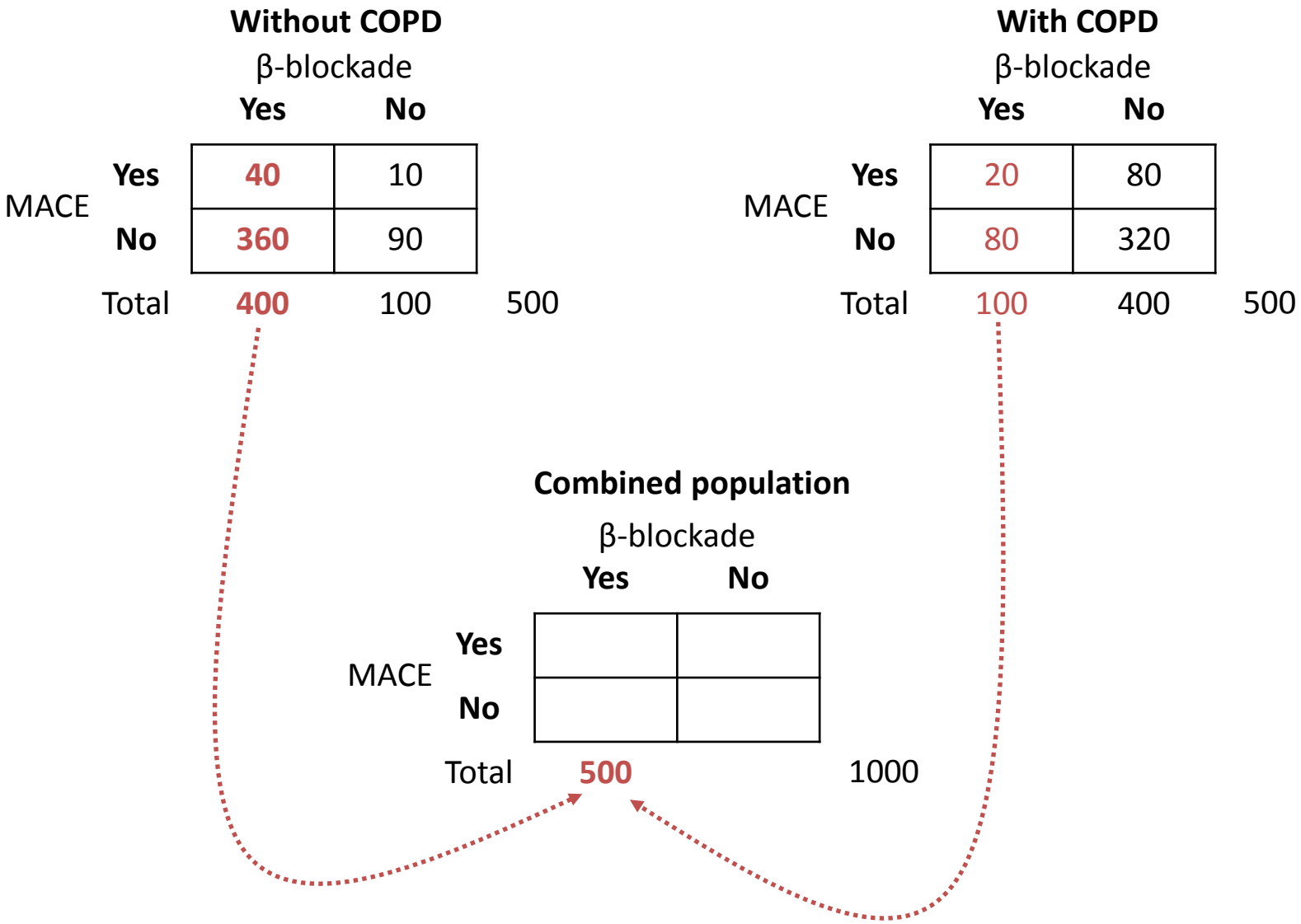
Combined population

		β-blockade: Yes	β-blockade: No
MACE	**Yes**		
	No		
	Total		

1000

So now let's combine the results. Adding together the 500 patients who have COPD and the 500 who do not we arrive at a total study population of 1,000.

Similarly, we have 500 patients who do receive β-blockade



So now let's combine the results. Adding together the 500 patients who have COPD and the 500 who do not we arrive at a total study population of 1,000. Similarly, we have 500 patients who do receive β-blockade and 500 who do not.

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500

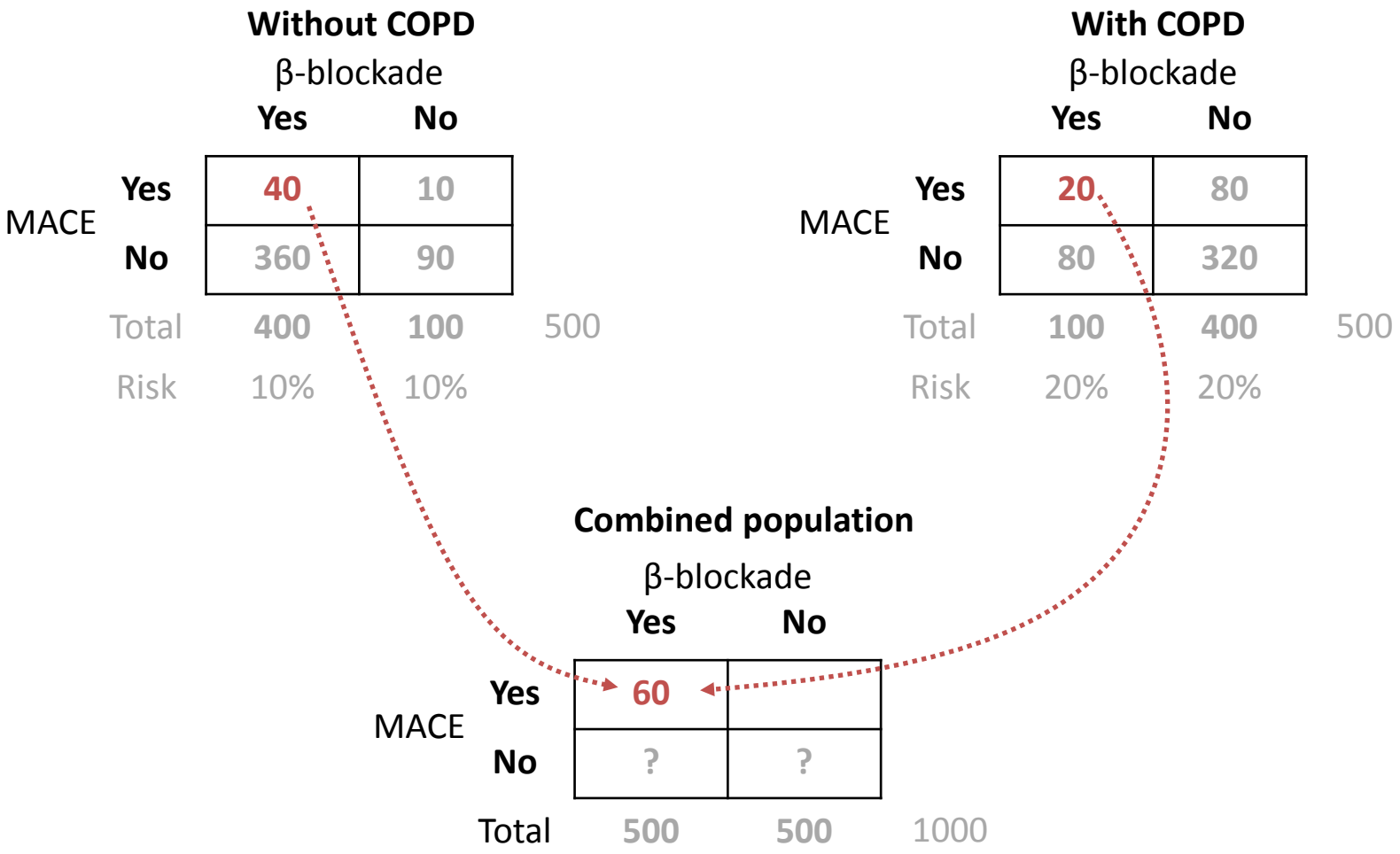
With COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	20	80	
	No	80	320	
	Total	100	400	500

Combined population

		β-blockade: Yes	β-blockade: No	
MACE	Yes			
	No			
	Total	500	500	1000

Given the results for the COPD sub-groups we can fill in the complete table by adding together the matching cells – for example, 40 patients without COPD and 20 patients with COPD experienced MACE despite β-blockade.



Now you can complete the table by filling in the remaining 3 cells.
Simply add together the contributions of patients with and without COPD.

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500
	Risk	10%	10%	

With COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	20	80	
	No	80	320	
	Total	100	400	500
	Risk	20%	20%	

Combined population

		β-blockade: Yes	β-blockade: No	
MACE	Yes	60	?	
	No	?	?	
	Total	500	500	1000

Are these the answers you got? Does everything add up?

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500
	Risk	10%	10%	

With COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	20	80	
	No	80	320	
	Total	100	400	500
	Risk	20%	20%	

Combined population

		β-blockade: Yes	β-blockade: No	
MACE	Yes	60	90	
	No	440	410	
	Total	500	500	1000

Are these the answers you got? Does everything add up?

Once you've convinced yourself that there are no "tricks", ask yourself – in the COPD sub-groups, does omitting β-blockade increase MACE risk?

Without COPD

MACE	β-blockade: Yes	β-blockade: No	
Yes	40	10	
No	360	90	
Total	400	100	500
Risk	10%	10%	

RR = ?

With COPD

MACE	β-blockade: Yes	β-blockade: No	
Yes	20	80	
No	80	320	
Total	100	400	500
Risk	20%	20%	

RR = ?

Combined population

MACE	β-blockade: Yes	β-blockade: No	
Yes	60	90	
No	440	410	
Total	500	500	1000
Risk	?	?	

We've answered this question before and the answer hasn't changed - "controlling" for COPD in sub-group specific analyses we see no evidence of a β-blockade effect. The RR = 1 among patients with or without COPD.

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500
	Risk	10%	10%	

RR = 1.0

With COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	20	80	
	No	80	320	
	Total	100	400	500
	Risk	20%	20%	

RR = 1.0

Combined population

		β-blockade: Yes	β-blockade: No	
MACE	Yes	60	90	
	No	440	410	
	Total	500	500	1000
	Risk	?	?	

Which is, of course, the answer you might expect to find when we simply add together the two sub-groups – complete the table to confirm your expectation.

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
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	Total	400	100	500
	Risk	10%	10%	

RR = 1.0

With COPD

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RR = 1.0

Combined population

		β-blockade: Yes	β-blockade: No	
MACE	Yes	60	90	
	No	440	410	
	Total	500	500	1000
	Risk	?	?	

RR = 1.0 ?

Which is, of course, the answer you might expect to find when we simply add together the two sub-groups – complete the table to confirm your expectation.

Is what you've observed what you expected? How did this happen?

Without COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500
	Risk	10%	10%	

RR = 1.0

With COPD

		β-blockade: Yes	β-blockade: No	
MACE	Yes	20	80	
	No	80	320	
	Total	100	400	500
	Risk	20%	20%	

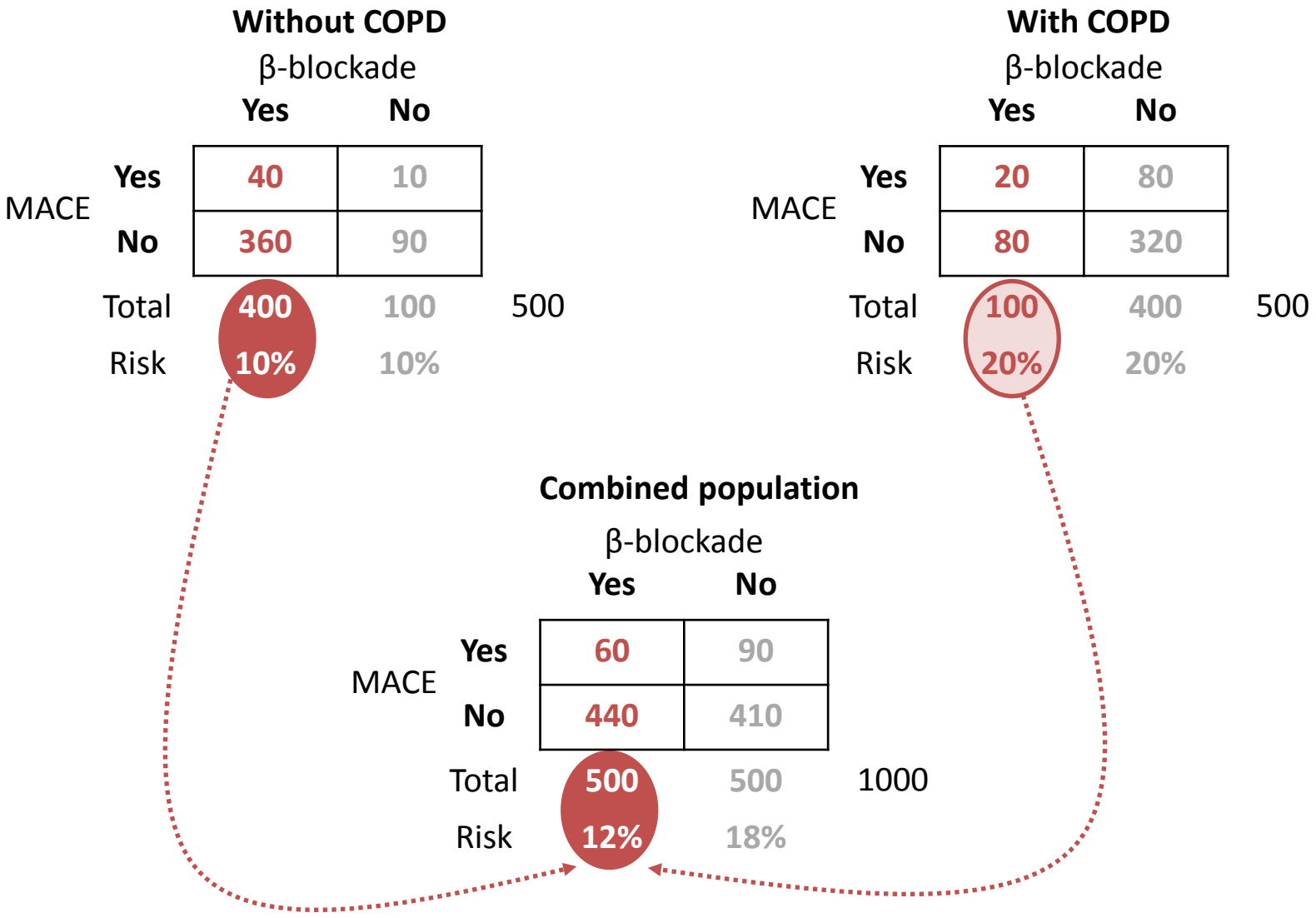
RR = 1.0

Combined population

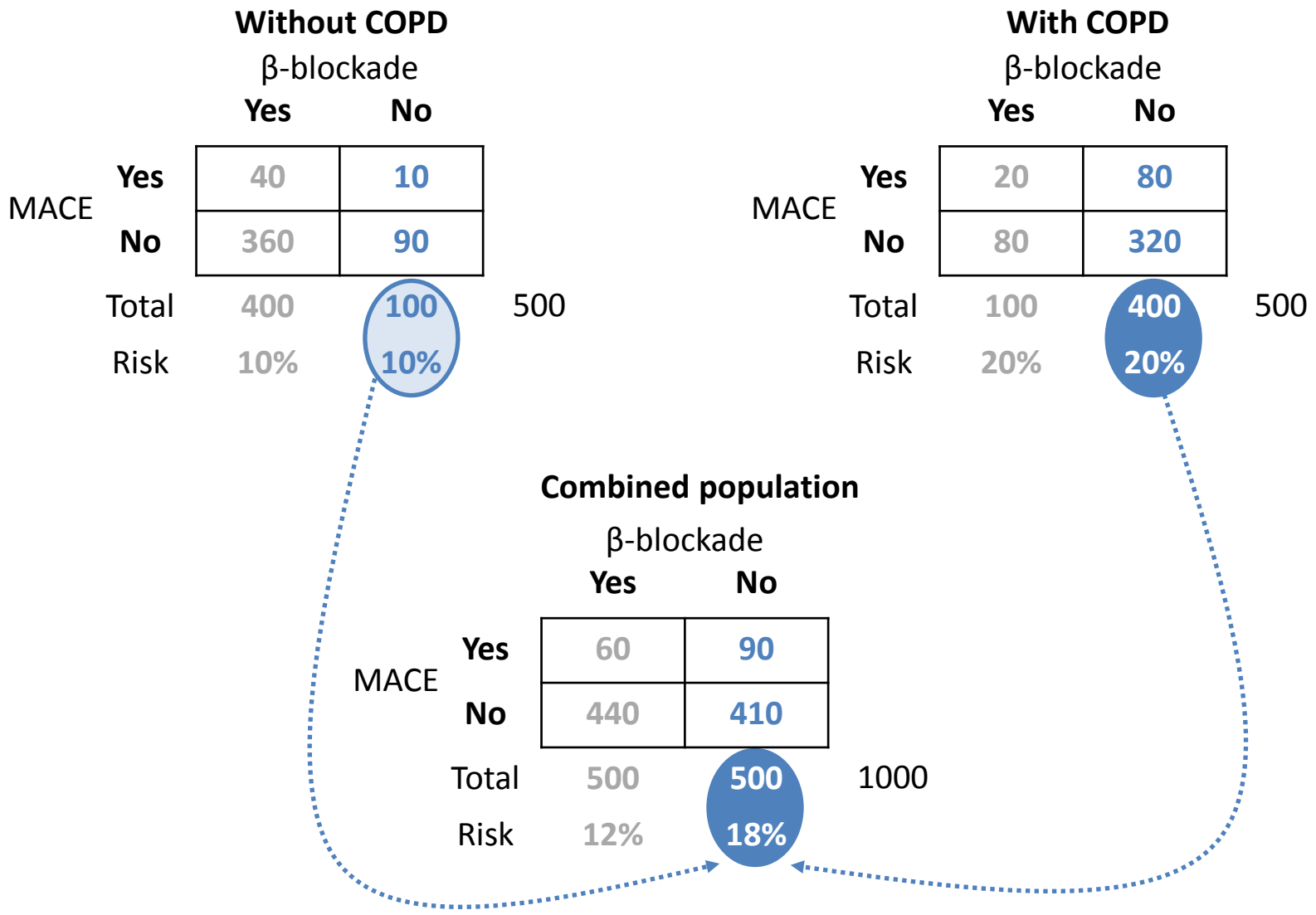
		β-blockade: Yes	β-blockade: No	
MACE	Yes	60	90	
	No	440	410	
	Total	500	500	1000
	Risk	12%	18%	

RR = 1.5

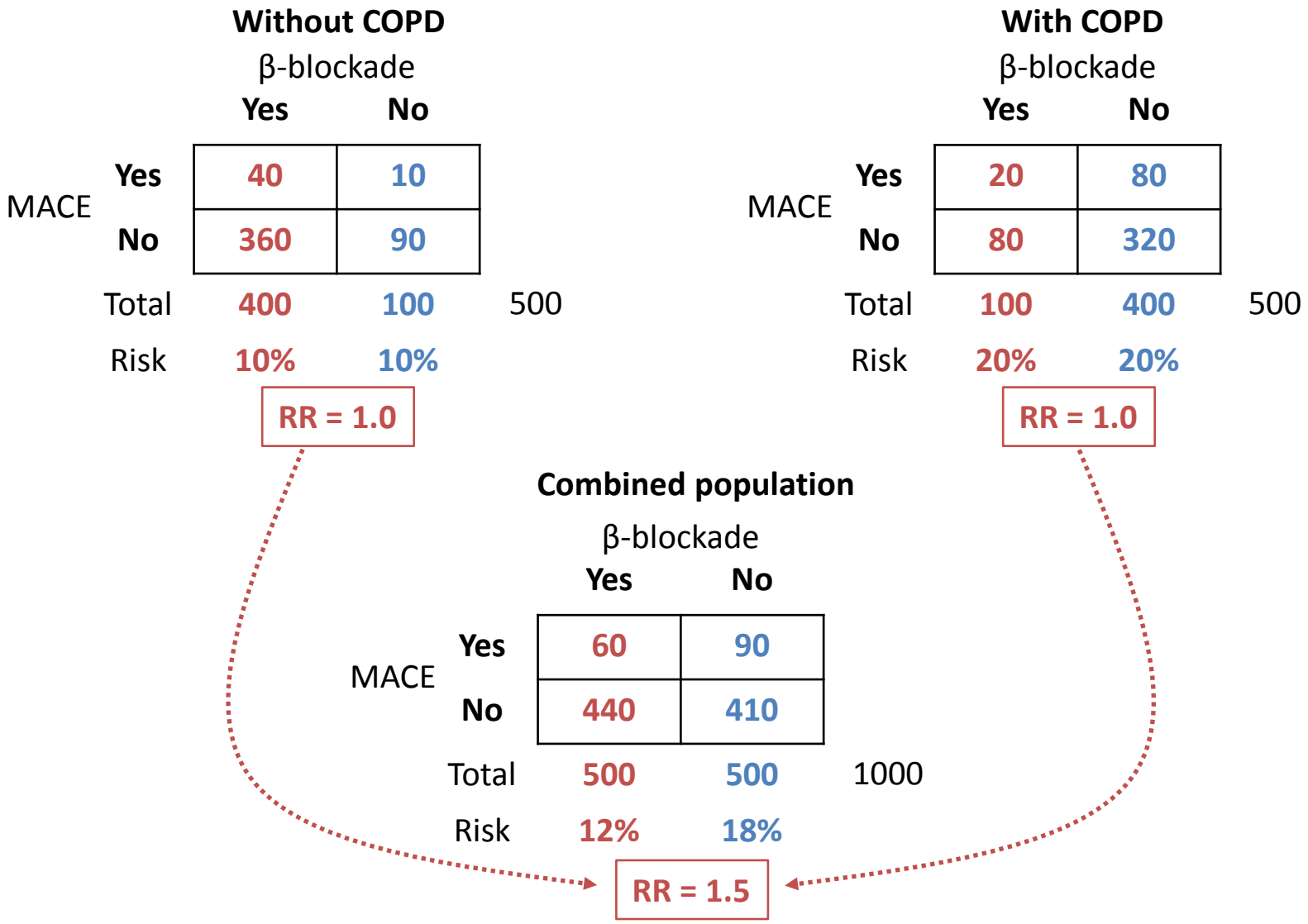
Blame it on confounding. In the study population as a whole, 20% of patients receiving β-blockade do have COPD while 80% don't. The "overall" risk in the β-blockade group is thus a *weighted average* dominated by the low risk experience of the 80% of patients who are free of COPD.



Conversely, among patients not receiving β-blockade, 80% do have COPD while only 20% don't. The "overall" risk in the no β-blockade group is thus a *weighted average* dominated by the high risk experience of patients who do have COPD.



The apparent benefit of β-blockade is simply an artifact of the company it keeps. It is the absence of COPD, not the presence of β-blockade, which reduces risk - β-blockade is simply serving as a *marker* for the absence of COPD.



One approach to controlling for confounding is to examine the pattern of associations in the specific sub-groups of interest (stratified analysis). More sophisticated approaches abound but all are based upon this same concept.

Without COPD

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MACE	Yes	40	10	
	No	360	90	
	Total	400	100	500
	Risk	10%	10%	

RR = 1.0

With COPD

		β-blockade: Yes	β-blockade: No	
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	Total	100	400	500
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RR = 1.0

Combined population

		β-blockade: Yes	β-blockade: No	
MACE	Yes	60	90	
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	Total	500	500	1000
	Risk	12%	18%	

RR = 1.5