General Internal Medicine Update 2020

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No disclosures

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Case #1

A 24 yo woman transfers care. Reports mild asthma with use of albuterol 2-3x/week, 2-3 noc. awake/month, 1 exacerbation requiring steroids in last year. She's happy with control and states is afraid of LTE of ICS and can't afford. The best recommendation is:

A. Continue prn albuterol and provide oral prednisone for exacerbation
B. Continue albuterol prn; add budesonide MDI 2 puffs bid as controller
C. Stop albuterol and recommend use of budesonide/formoterol as needed instead of prn albuterol
D. Recommend a LABA such as salmeterol or formoterol as primary controller rx
E. Recommend continuing albuterol prn and add budesonide + formoterol bid as controller rx

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 MAY 17, 2018 VOL. 378 NO. 20

Inhaled Combined Budesonide–Formoterol as Needed in Mild Asthma

Paul M. O'Byrne, M.B., J. Mark FitzGerald, M.D., Eric D. Bateman, M.D., Peter J. Barnes, M.D., Nanshan Zhong, Ph.D., Christina Keen, M.D., Carin Jorup, M.D., Rosa Lamarca, Ph.D., Stefan Ivanov, M.D., Ph.D., and Helen K. Reddel, M.B., B.S., Ph.D.

ORIGINAL ARTICLE

Controlled Trial of Budesonide–Formoterol as Needed for Mild Asthma

Richard Beasley, D.Sc., Mark Holliday, B.Sc., Helen K. Reddel, Ph.D., Irene Braithwaite, Ph.D., Stefan Ebmeier, B.M., B.Ch., Robert J. Hancox, M.D., Tim Harrison, M.D., Claire Houghton, B.M., B.S., Karen Oldfield, M.B., Ch.B., Alberto Papi, M.D., Ian D. Pavord, F.Med.Sci., Mathew Williams, Dip.Ex.Sci., and Mark Weatherall, F.R.A.C.P., for the Novel START Study Team*

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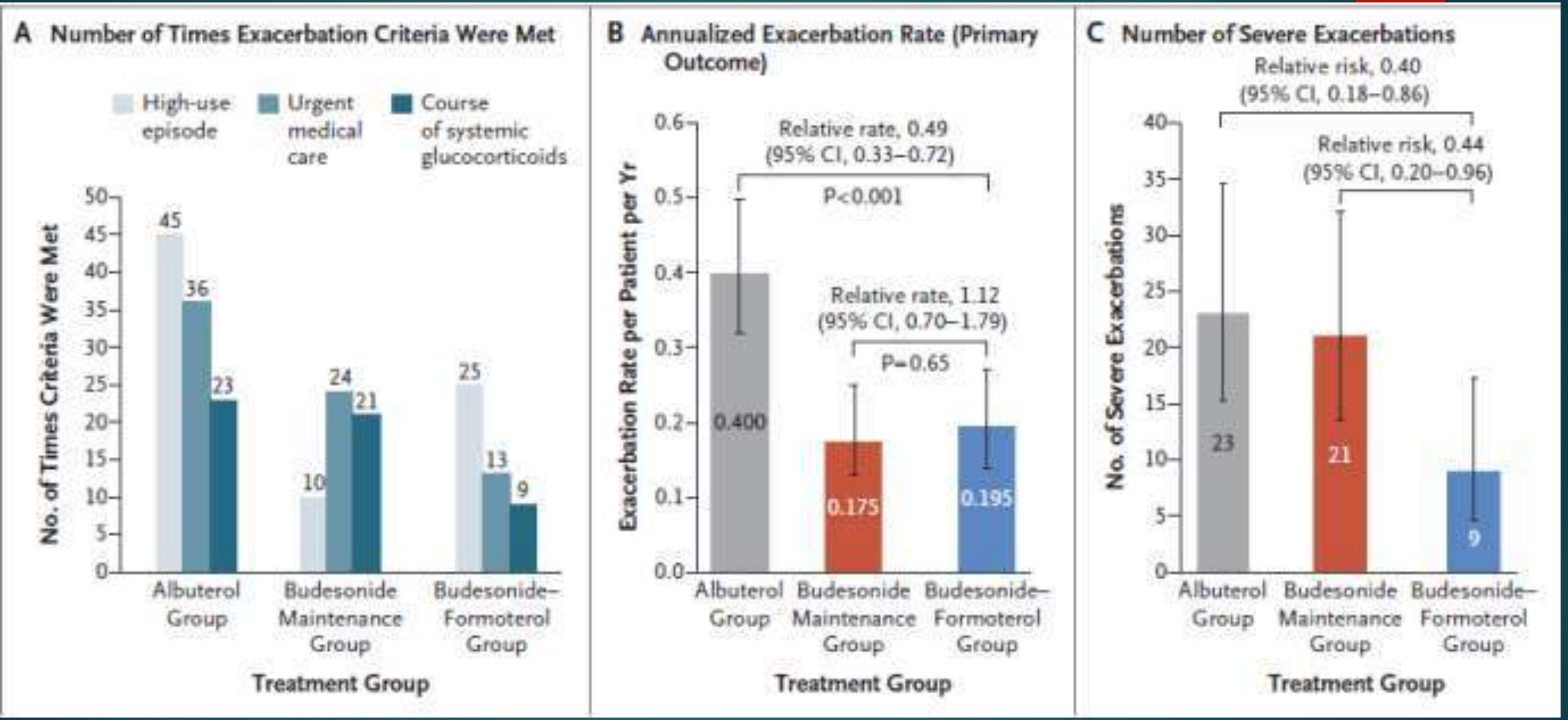
Mild Asthma Bkg

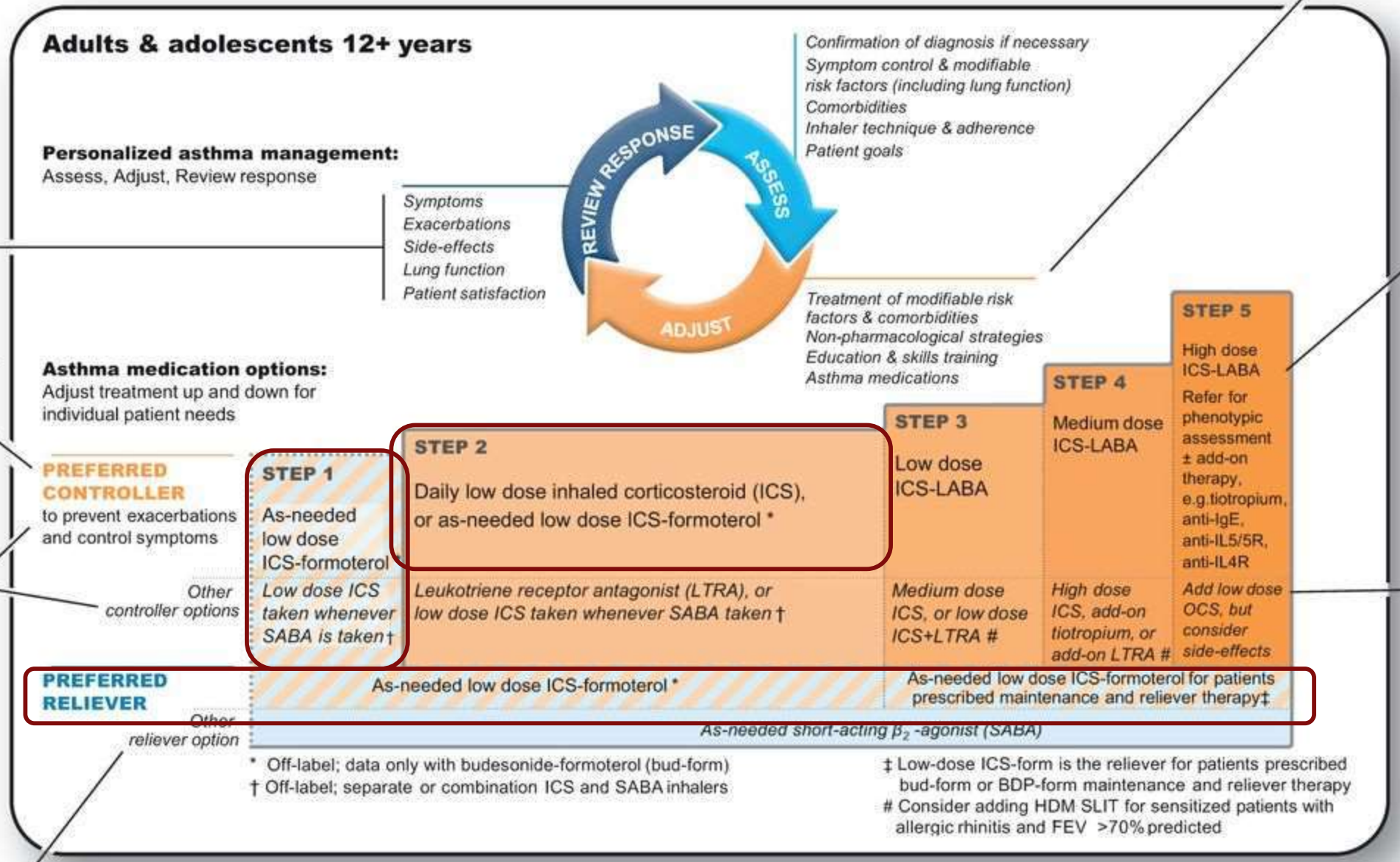
- Mild persistent asthma = > 2 days/wk, nt time awakening > 2x/mo, SABA > 2x/wk, minor interference with activity
- 25 million in US with asthma
- 50-70% of asthmatics = mild persistent
- Recommended rx = LD ICS with prn rescue SABA
- ICS compliance thought to be poor
- Most use prn SABA only
- 30-40% of emergency care exacerbations = mild asthmatics

START Study Background

- SYGMA = revolution in approach to mild asthma—use ICS + Formoterol as rescue—no maintenance med.
- SYGMA may not parallel real world experience
- START trial
  - 52 week randomized open label mild asthmatics
  - 3 arms—Albuterol prn only, Budesonide daily + prn Albuterol, Budesonide/Formoterol prn only
  - 1^0 endpoint = annualized rate of exacerbation (urgent med consult, any systemic steroids, > 16 albut or 8 budes/formot in 24 hours)
  - 2^0 endpoint = severe exacerbation = systemic glucocorticoids x 3d or hospitalization


A Number of Times Exacerbation Criteria Were Met
High-use episode
Urgent medical care
Course of systemic glucocorticoids
No. of Times Criteria Were Met
50
45
40
35
30
25
20
15
10
5
0
45
36
23
10
24
21
25
13
9
Albuterol Group
Budesonide Maintenance Group
Budesonide–Formoterol Group
Treatment Group
B Annualized Exacerbation Rate (Primary Outcome)
Exacerbation Rate per Patient per Yr
0.6
0.5
0.4
0.3
0.2
0.1
0.0
Relative rate, 0.49
(95% CI, 0.33–0.72)
P<0.001
Relative rate, 1.12
(95% CI, 0.70–1.79)
P=0.65
0.400
0.175
0.195
Albuterol Group
Budesonide Maintenance Group
Budesonide–Formoterol Group
Treatment Group
C Number of Severe Exacerbations
Relative risk, 0.40
(95% CI, 0.18–0.86)
Relative risk, 0.44
(95% CI, 0.20–0.96)
No. of Severe Exacerbations
40
35
30
25
20
15
10
5
0
23
21
9
Albuterol Group
Budesonide Maintenance Group
Budesonide–Formoterol Group
Treatment Group

Personalised asthma management



A holistic approach – not just symptom control

ICS-containing controller is recommended across all severities to reduce exacerbation risk

"Preferred" and "other" options are provided at each step, based on evidence

SABA is not a preferred reliever because of the risks of SABA-only treatment, including if adherence is poor

See 2019 GINA Severe Asthma Pocket Guide for more details about Steps 4–5

Maintenance OCS is not a preferred option at Step 5 because of serious side-effects

SYGMA/START Conclusions

- Mild persistent asthma common
- Patients typically prefer prn instead of daily maintenance med
- Low dose ICS + formoterol is now the preferred rescue agent
- Think first about ICS + Formoterol “rescue” instead of maintenance ICS
- Not validated in more severe asthma.

Case #2

A 58 yo man with COPD presents with 2 days of increased SOB, cough, and sig increase in thick yellow sputum. Exam show SaO2 = 93%, T = 99^0 F, BP = 135/85, lungs with scattered rhonchi, minimal wheeze, prolonged expiration. CXR no infiltrate. He had negative COVID test yesterday. You elect to begin corticosteroids and increase his bronchodilator regimen. In selecting antibiotic therapy for this patient the next best step would be:

A. Begin Azithromycin 500/250 x 5 days
B. Withhold antibiotics until fever or other clinical deterioration occurs
C. Obtain a CRP level
D. Begin Ciprofloxacin 500 mg bid x 7d
E. Obtain a sputum culture

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The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JULY 11, 2019 VOL. 381 NO. 2

C-Reactive Protein Testing to Guide Antibiotic Prescribing for COPD Exacerbations

Christopher C. Butler, F.Med.Sci., David Gillespie, Ph.D., Patrick White, M.D., Janine Bates, M.Phil., Rachel Lowe, Ph.D., Emma Thomas-Jones, Ph.D., Mandy Wootton, Ph.D., Kerenza Hood, Ph.D., Rhiannon Phillips, Ph.D., Hasse Melbye, Ph.D., Carl Llor, Ph.D., Jochen W.L. Cals, M.D., Ph.D., Gurudutt Naik, M.B., M.S., M.P.H., Nigel Kirby, M.A., Micaela Gal, D.Phil., Evgenia Riga, M.Sc., and Nick A. Francis, Ph.D.

COPD & Antibiotics—PACE Background

- > 6% of Americans have COPD.
- ½ COPDers →exacerbation yearly → steroids and abx.
- > 80% exac rxd with abx.
- Abx based on symp of > sputa volume, > purulence, > dyspnea---2 of 3 usually → abx.
- What if could more reliably predict bacterial infectious precipitator?
- Hypothesis: CRP during acute exac could safely < abx prescript.

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COPD & ABX—PACE Trial

- Multicenter, random, open label, controlled trial 2015-2017--86 practices from UK—653 patients.
- 1:1 assignment--usual care vs usual + CRP. Tele & Office f/u.
- Guideline: CRP < 20 benefit unlikely, 20-40 = maybe beneficial, >40 likely beneficial.
- MDs instructed: evaluate abx prescrip globally but include CRP in thought process (if provided).
- Prime outcome = reported use of abx, & COPD related health status questionnaire.

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COPD & Antibiotics—PACE Results

- CRP Results:
  - < 20 = 76%
  - 20-40 = 12%
  - > 40 = 12%
- Anthonesin Criteria Present (sputa, purulence, dysp)
  - 1 = 24%
  - 2 = 30.5%
  - 3 = 45.3%

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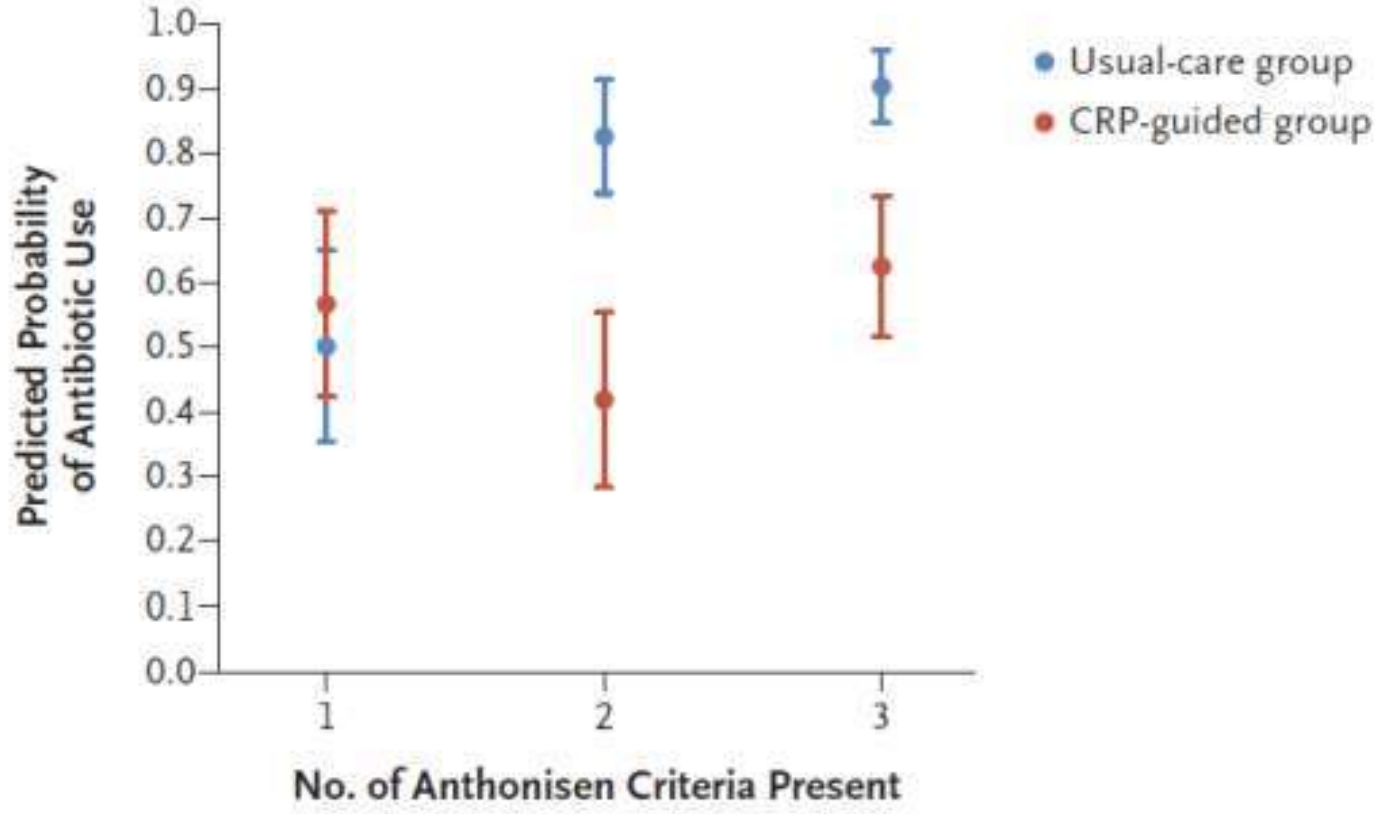

Figure 2. Differential Effect of the Interventions on the Use of Antibiotics during the First 4 Weeks.

Shown is the predicted probability of antibiotic use for acute exacerbations of COPD during the first 4 weeks according to the number of Anthonisen criteria present. The Anthonisen criteria include increased dyspnea, increased sputum volume, and increased sputum purulence. I bars denote 95% confidence intervals.[29]

COPD & Abx—PACE Conclusions

- CRP POC test→ 22% reduction in abx @ initial visit
- 4 week abx use = 59.1% vs. 79.7%
- No impact when 1 exacerbation criteria present.
- Greatest impact when 2 criteria present: 85%→45%.
- Moderate impact when 3 present: 95% → 65%.
- No difference in COPD questionnaire nor adverse events.
- Use of POC CRP can reduce COPD abx by 20%.

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Case #3

62 yo woman presents for CVD risk reduction. She had AWMI 2 years ago, had PTCA, symptom free since. Meds: Atorvastatin 40, lisinopril 20, ASA 81. BP is 120/70. Lipids = Tchol 180 mg/dl, HDL = 50, LDL = 62, TG = 175. She seeks your advice about fish oil & reducing her risk of CV death.

A. Recommend OTC EPA/DHA 1 g daily
B. Recommend niacin 2g daily instead of fish oil
C. Advise fresh fish but not oil—oil not found to reduce CV event risk
D. Recommend prescription fish oil 2g bid—Vascepa
E. Recommend garlic, red yeast rice, astralagus, and bergamot instead of fish oil

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Marine n–3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

JoAnn E. Manson, M.D., Dr.P.H., Nancy R. Cook, Sc.D., I-Min Lee, M.B., B.S., Sc.D., William Christen, Sc.D., Shari S. Bassuk, Sc.D., Samia Mora, M.D., M.H.S., Heike Gibson, Ph.D., Christine M. Albert, M.D., M.P.H., David Gordon, M.A.T., Trisha Copeland, M.S., R.D., Denise D'Agostino, B.S., Georgina Friedenberg, M.P.H., Claire Ridge, M.P.H., Vadim Bubes, Ph.D., Edward L. Giovannucci, M.D., Sc.D., Walter C. Willett, M.D., Dr.P.H., and Julie E. Buring, Sc.D., for the VITAL Research Group*

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JANUARY 3, 2019 VOL. 380 NO. 1

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, M.D., M.P.H., P. Gabriel Steg, M.D., Michael Miller, M.D., Eliot A. Brinton, M.D., Terry A. Jacobson, M.D., Steven B. Ketchum, Ph.D., Ralph T. Doyle, Jr., B.A., Rebecca A. Juliano, Ph.D., Lixia Jiao, Ph.D., Craig Granowitz, M.D., Ph.D., Jean-Claude Tardif, M.D., and Christie M. Ballantyne, M.D., for the REDUCE-IT Investigators*

Fish Oil & CVD Background

- CVD risk persists despite excellent chol control
- Numerous observational studies: 1^0 prevention benefit
- 2^0 prevention studies → inconsistent results
- No large 1^0 prevention randomized trials
- Vitamin D 2000 IU & Omega-3 FA 1g/d = VITAL Trial
  - 25,871 men > 50 women > 55
  - 50% HTN—37% lipid meds
- Purified EPA = Icosapent ethyl 2g bid = REDUCE IT
  - 8,179 with estab CVD or DM & risk + TG > 150

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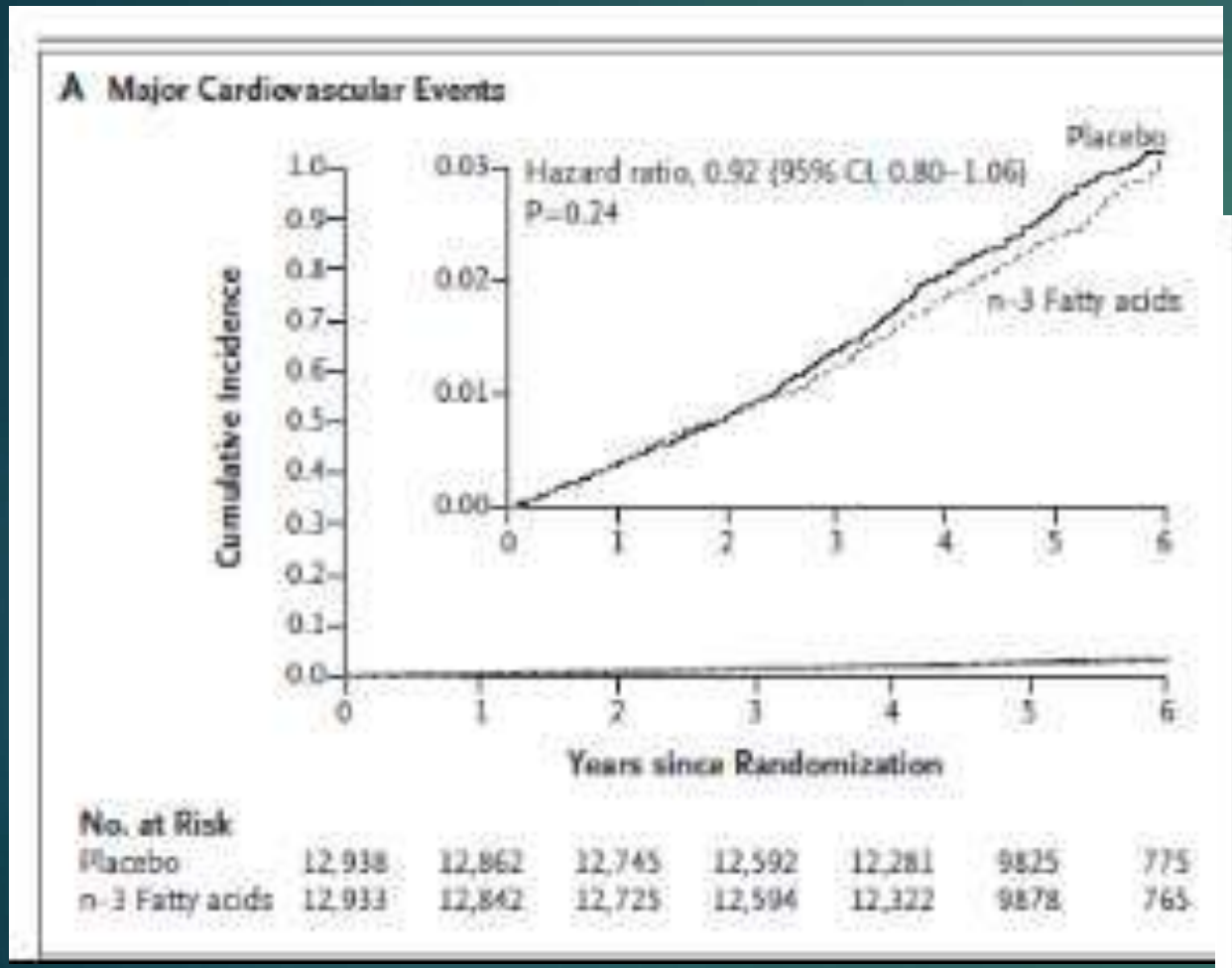
VITAL Findings—Omega 3 FA



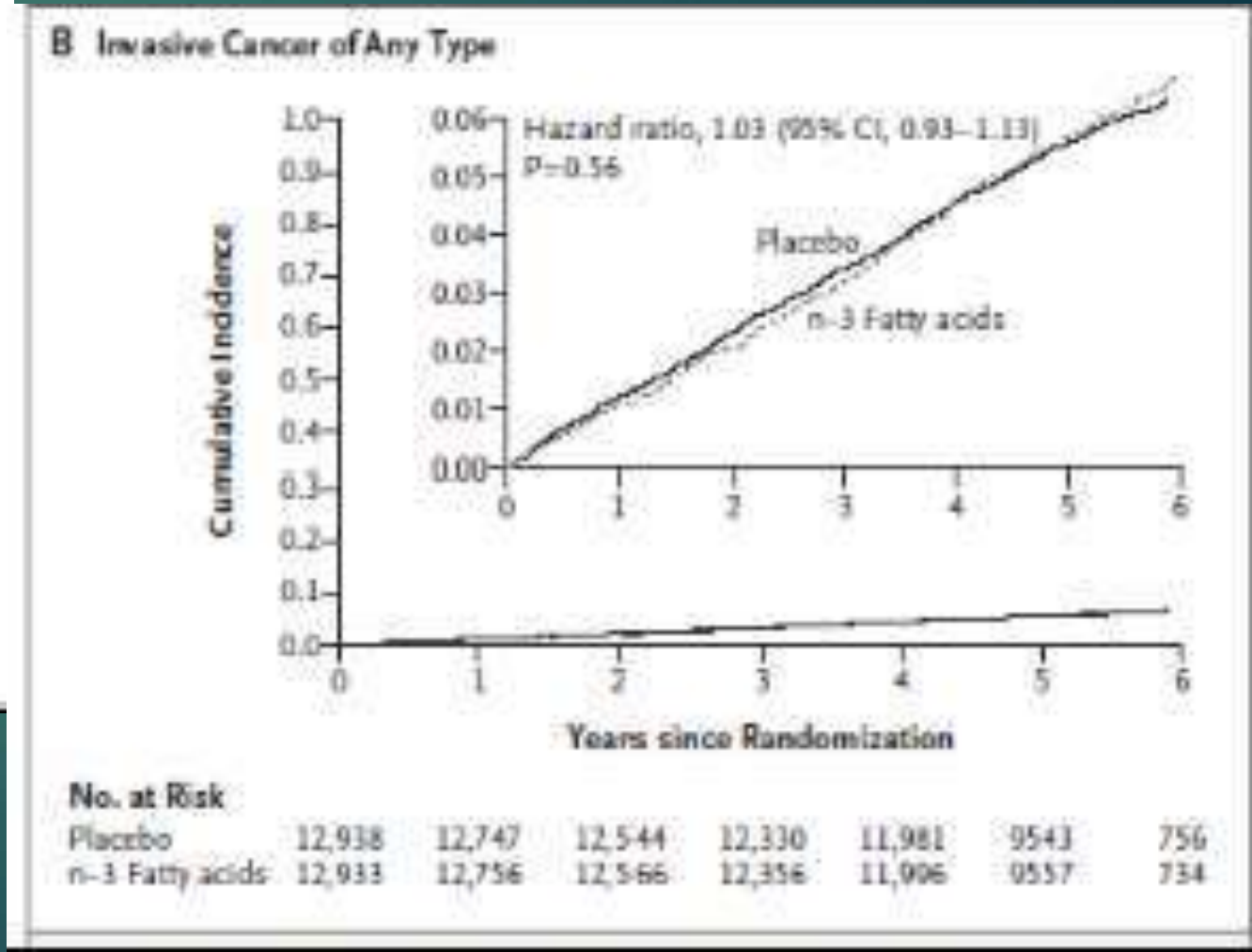


Table 2. Hazard Ratios and 95% Confidence Intervals for the Primary, Secondary, and Other End Points, According to Randomized Assignment to n-3 Fatty Acids or Placebo, in Intention-to-Treat Analyses.*

End Point	n-3 Group (N=12,933)	Placebo Group (N=12,938)	Hazard Ratio (95% CI)
	no. of participants with event		
Cardiovascular disease			
Primary end point: major cardiovascular event†	386	419	0.92 (0.80–1.06)
Cardiovascular event in expanded composite end point‡	527	567	0.93 (0.82–1.04)
Total myocardial infarction	145	200	0.72 (0.59–0.90)
Total stroke	148	142	1.04 (0.83–1.31)
Death from cardiovascular causes	142	148	0.96 (0.76–1.21)
Other cardiovascular end point§			
PCI	162	208	0.78 (0.63–0.95)
CABG	85	86	0.99 (0.73–1.33)
Total coronary heart disease¶	308	370	0.83 (0.71–0.97)
Ischemic stroke	111	116	0.96 (0.74–1.24)
Hemorrhagic stroke	25	19	1.32 (0.72–2.39)
Death from coronary heart disease	37	49	0.76 (0.49–1.16)
Death from myocardial infarction	13	26	0.50 (0.26–0.97)
Death from stroke	22	20	1.10 (0.60–2.01)

VITAL Conclusions

- Omega 3 FA supplements → no CV composite benefit
- No stroke benefit, No CV Death benefit
- No invasive CA benefit
- → 28% RRR in MI . 0.43% ARR in MI NNT = 233 x 5.3 years
- Apparent minimal benefit from Fish Oil in 1^0 prevention

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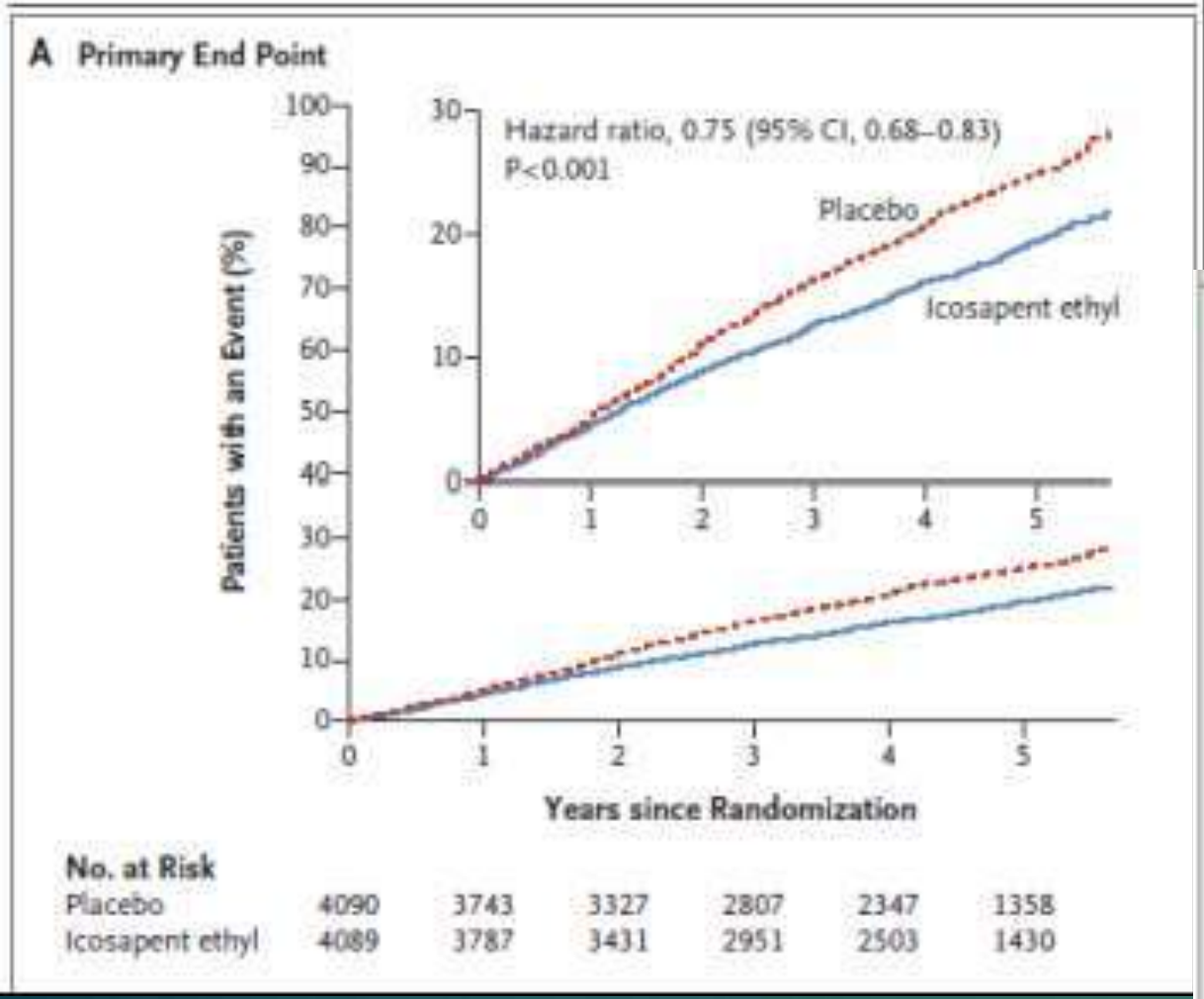
REDUCE IT—Findings

2g bid—known CVD



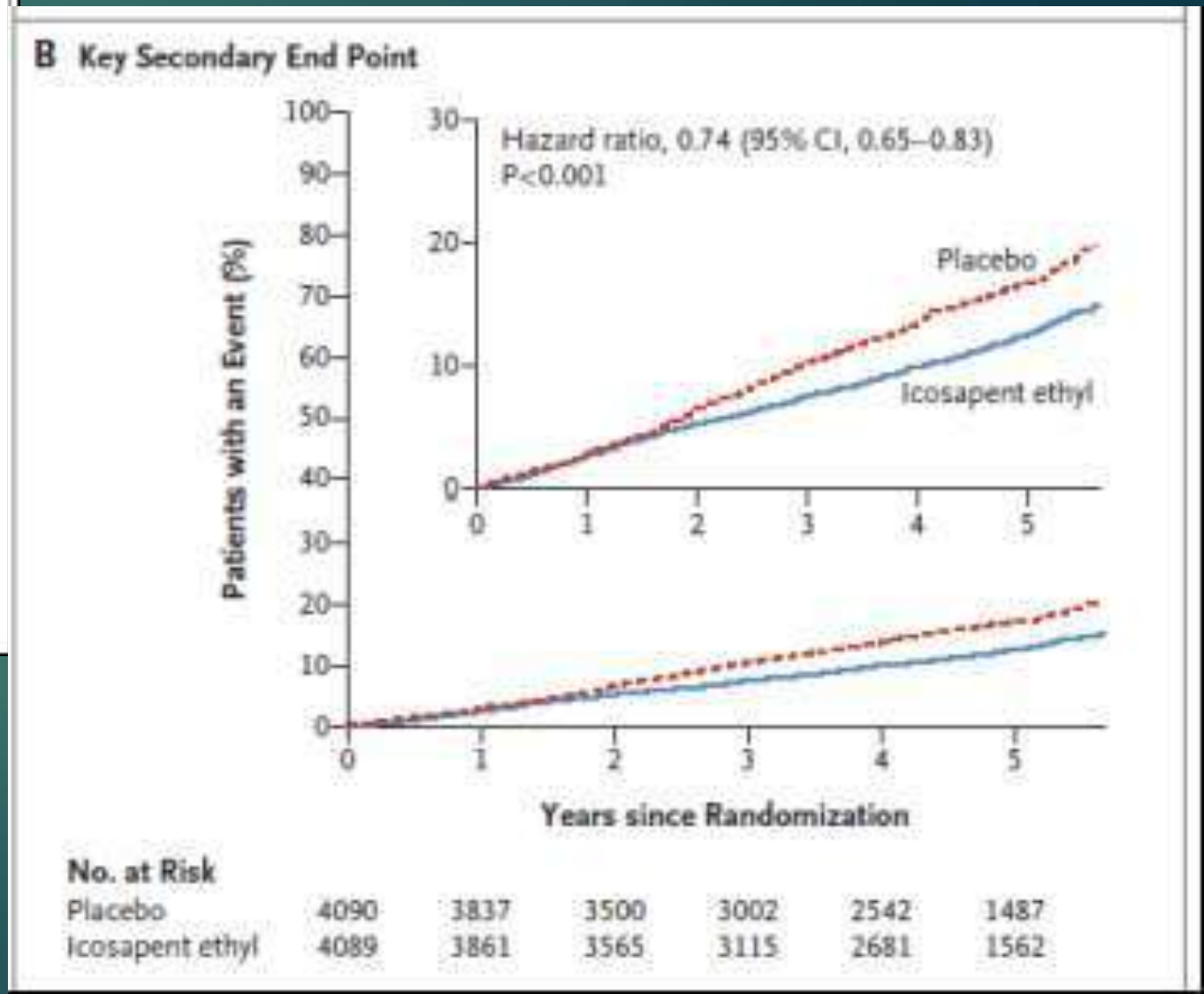


Figure 1. Cumulative Incidence of Cardiovascular Events.

Panel A shows the Kaplan–Meier event curves for the primary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina in the icosapent ethyl group and the placebo group, in a time-to-event analysis. Panel B shows the Kaplan–Meier event curves for the key secondary efficacy composite end point of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke in the two trial groups, in a time-to-event analysis. In each panel, the

End Point	Icosapent Ethyl (N=4089)	Placebo (N=4090)	Hazard Ratio (95% CI)	P Value
	no. of patients with event (%)			
Primary composite	705 (17.2)	901 (22.0)	0.75 (0.68–0.83)	<0.001
Key secondary composite	459 (11.2)	606 (14.8)	0.74 (0.65–0.83)	<0.001
Cardiovascular death or nonfatal myocardial infarction	392 (9.6)	507 (12.4)	0.75 (0.66–0.86)	<0.001
Fatal or nonfatal myocardial infarction	250 (6.1)	355 (8.7)	0.69 (0.58–0.81)	<0.001
Urgent or emergency revascularization	216 (5.3)	321 (7.8)	0.65 (0.55–0.78)	<0.001
Cardiovascular death	174 (4.3)	213 (5.2)	0.80 (0.66–0.98)	0.03
Hospitalization for unstable angina	108 (2.6)	157 (3.8)	0.68 (0.53–0.87)	0.002
Fatal or nonfatal stroke	98 (2.4)	134 (3.3)	0.72 (0.55–0.93)	0.01
Death from any cause, nonfatal myocardial infarction, or nonfatal stroke	549 (13.4)	690 (16.9)	0.77 (0.69–0.86)	<0.001
Death from any cause	274 (6.7)	310 (7.6)	0.87 (0.74–1.02)	—

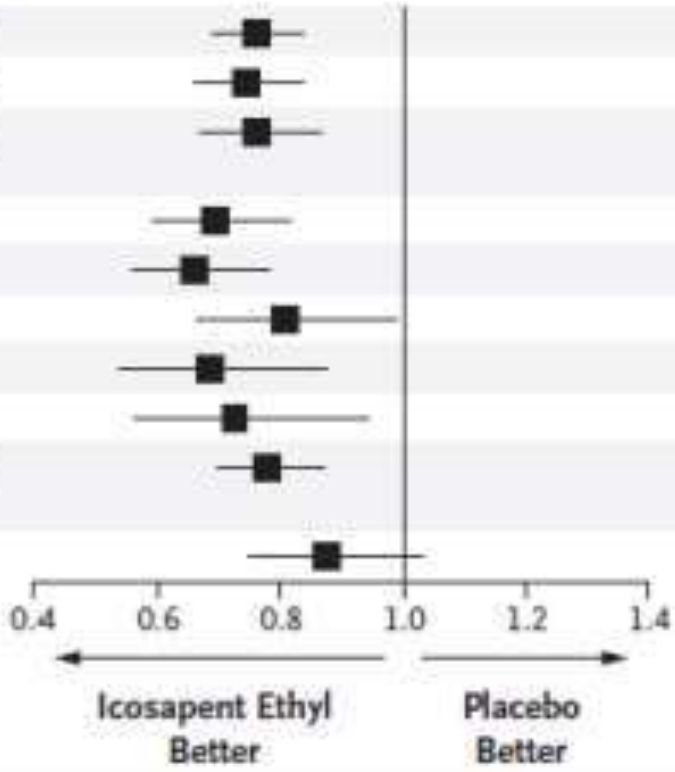


Figure 4. Hierarchical Testing of End Points.

Shown is the prespecified plan for hierarchical testing of end points. The rates of all end points up to death from any cause were significantly lower in the icosapent ethyl group than in the placebo group.

VITAL v. REDUCE IT—How reconcile

- VITAL = Primary Prevention. REDUCE IT = Secondary--mostly
- VITAL = All Patients. REDUCE IT = only > TG
- VITAL = Low dose Omega 3. REDUCE IT = High dose enriched
- Reasonable conclusions:
  - Limited benefit of OTC Omega 3 in Primary Prevention
  - Substantial benefit in high dose enriched EPA in > risk pop with > TG.

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JAMA | Original Investigation

Association of Unrecognized Obstructive Sleep Apnea With Postoperative Cardiovascular Events in Patients Undergoing Major Noncardiac Surgery

Matthew T. V. Chan, MBBS, PhD; Chew Yin Wang, MBChB; Edwin Seet, MBBS, MMed; Stanley Tam, MD; Hou Yee Lai, MBBS; Eleanor F. F. Chew, MBBS; William K. K. Wu, PhD; Benny C. P. Cheng, MBBS; Carmen K. M. Lam, MBBS; Timothy G. Short, MD; David S. C. Hui, MD; Frances Chung, MBBS; for the Postoperative Vascular Complications in Unrecognized Obstructive Sleep Apnea (POSA) Study Investigators

POSA Background

- Post Operative Vascular Complications in Unrecognized Sleep Apnea
- OSA = Cyclic alternation between pharyngeal collapse and arousal
- Most common sleep breathing disorder
- General anesthetics, sedatives, narc analgesics→ exacerbate
- Hypothesis: Unrecognized OSA would be associated with > CV complications in surgical patients

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POSA Methods

- Multicenter prospective cohort-- major non-CV surg—1218 enrolled
- All undergo portable overnight study on ward or at home < 30d b-4 surg
- Severity based on REI:
  - < 5 normal
  - 5-15 mild
  - 15-30 mod
  - >30 severe
- Followed 30 d
- 1^0 endpoint composite:
  - MI
  - CV Death
  - CHF
  - VTE
  - AF
  - New stroke
- 67.6% had unrecognized OSA; 11.2% had severe OSA

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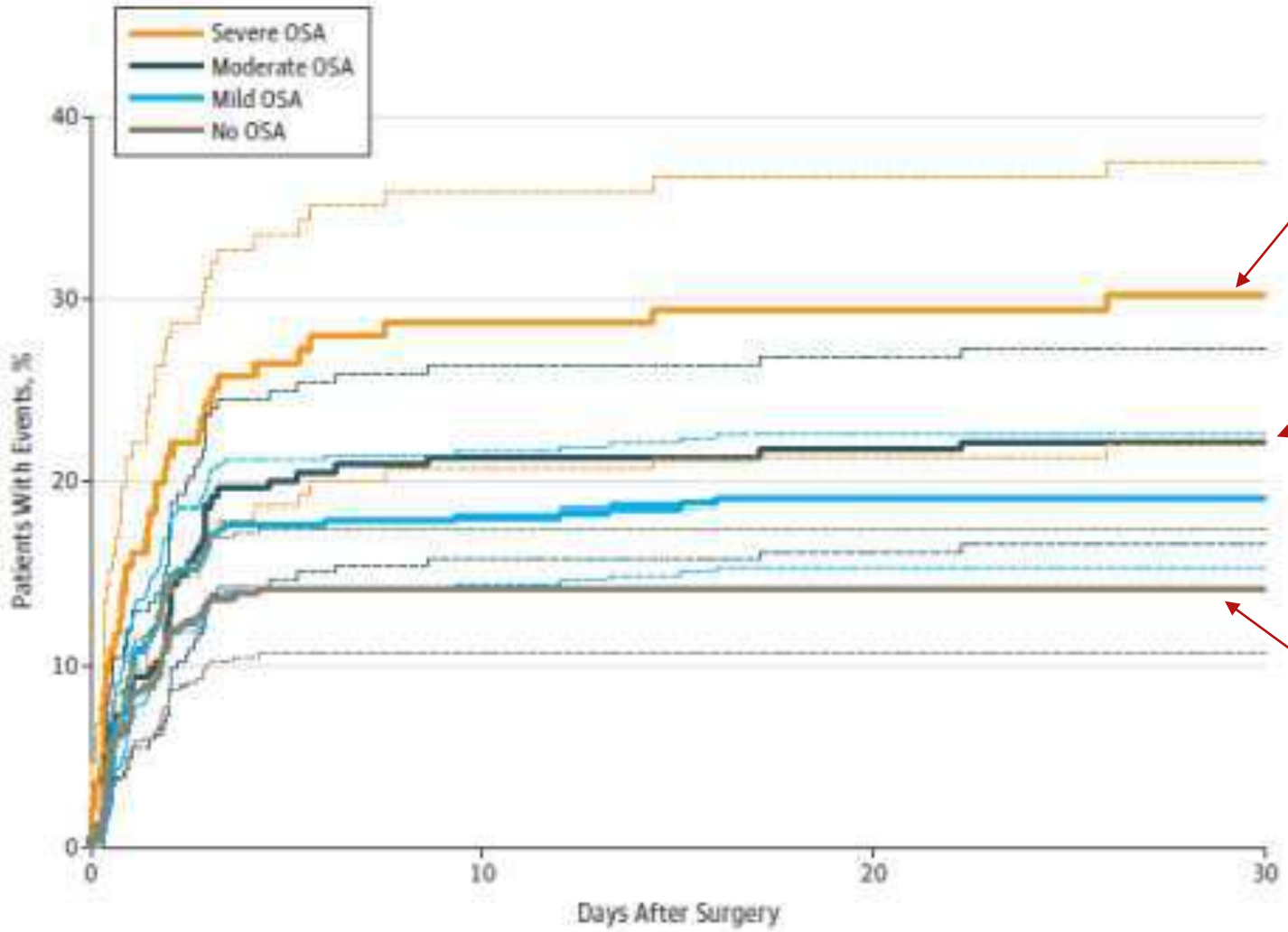
Figure 2. Kaplan-Meier Estimates of the Primary Composite Outcome (Death, Myocardial Injury, Congestive Heart Failure, Thromboembolism, New Atrial Fibrillation, and Stroke at 30 Days After Surgery)



No. at risk				
Severe OSA	136	98	97	95
Moderate OSA	235	186	185	183
Mild OSA	452	371	367	366
No OSA	395	340	340	340

Severe OSA

Mod OSA

No OSA

Dashed lines indicate 95% confidence intervals. Median follow-up time was 30 days (interquartile range [IQR], 30-32) for patients with severe obstructive sleep apnea (OSA), 30 days (IQR, 30-32) for those with moderate OSA; 30 days (IQR, 30-31) for those with mild OSA, and 30 days (IQR, 30-33) for those with no OSA.

Post Hoc Analysis of Components of Primary Outcome					
Cardiac death[a]					
Severe OSA	6/136 (4.4)	17.90 (2.16-148.69)	.008	13.56 (1.60-114.19)	.02
Moderate OSA	8/235 (3.4)	13.57 (1.70-108.53)	.01	10.56 (1.31-84.89)	.03
Mild OSA	2/452 (0.4)	1.75 (0.16-19.31)	.65	1.43 (0.93-15.93)	.77
No OSA	1/395 (0.3)	1 [Reference]		1 [Reference]	
Myocardial injury[b]					
Severe OSA	35/124 (28.2)	2.11 (1.37-3.24)	.001	1.80 (1.17-2.77)	.008
Moderate OSA	41/220 (18.6)	1.34 (0.89-2.02)	.16	1.20 (0.80-1.81)	.39
Mild OSA	77/416 (18.5)	1.32 (0.93-1.88)	.12	1.37 (0.93-1.89)	.12
No OSA	52/364 (14.3)	1 [Reference]		1 [Reference]	
Congestive heart failure[c]					
Severe OSA	8/136 (5.9)	7.86 (2.09-29.62)	.002	7.04 (1.86-26.66)	.004
Moderate OSA	6/235 (2.6)	3.39 (0.85-13.57)	.08	3.12 (0.78-12.50)	.10
Mild OSA	4/452 (0.9)	1.17 (0.26-5.20)	.84	1.10 (0.25-4.97)	.89
No OSA	3/395 (0.8)	1 [Reference]		1 [Reference]	
New-onset atrial fibrillation[e]					
Severe OSA	7/136 (5.1)	4.13 (1.31-13.02)	.02	3.75 (1.19-11.87)	.03
Moderate OSA	7/235 (3.0)	2.37 (0.75-7.45)	.14	2.18 (0.69-6.89)	.82
Mild OSA	11/452 (2.4)	1.75 (0.60-5.11)	.31	1.89 (0.66-5.46)	.24
No OSA	5/395 (1.3)	1 [Reference]		1 [Reference]	

Secondary Outcomes					
Unplanned admission or readmission to ICU[g]					
Severe OSA	15/136 (11.0)	OR, 6.87 (2.74-17.24)	<.001	OR, 6.60 (2.61-16.70)	<.001
Moderate OSA	20/235 (8.5)	OR, 5.16 (2.15-12.39)	<.001	OR, 4.99 (2.06-12.06)	<.001
Mild OSA	26/452 (5.8)	OR, 3.38 (1.45-7.88)	.005	OR, 3.55 (1.52-8.31)	.005
No OSA	7/395 (1.8)	1 [Reference]		1 [Reference]	
Unplanned tracheal intubation or postoperative lung ventilation[h]					
Severe OSA	18/136 (13.2)	OR, 6.54 (2.86-14.95)	<.001	OR, 6.16 (2.51-15.16)	<.001
Moderate OSA	31/235 (13.2)	OR, 6.52 (3.04-13.95)	<.001	OR, 6.26 (2.85-13.75)	<.001
Mild OSA	23/452 (5.1)	OR, 2.29 (1.05-5.03)	.04	OR, 2.28 (1.04-5.03)	.04
No OSA	9/395 (2.3)	1 [Reference]		1 [Reference]	

POSA Conclusions

- Unsuspected OSA extremely common
- Severe OSA associated with sig > CV events
  - 30.1% event rate in severe, HR 2.23
  - 4.4% cardiac death; HR 13.56 (Mod OSA 3.4%; HR 10.56)
  - 28.2% MI; HR 1.80
  - 5.9% CHF; HR 7.04
  - 11% Unplanned ICU; HR 6.60
- OSA can be easily detected with portable device
- Not intervention trial--Best Rx unknown:
  - Delay elective surg and begin CPAP?
  - Reduce Narc/Sed
  - HOB Elev
  - Continuous O_2 & CO_2 monitors
- Optimization of OSA may be as important as DM optimization and CV risk reduction.

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Case #4

A 60 yo woman presents seeking routine preventive care. She is healthy, takes no meds, menopause 10 years ago, neg mammogram 3 months ago with moderately heterogeneously dense tissue. + FH for breast cancer in mother at 55 and a personal hx of a benign breast biopsy 5 years ago and unprovoked DVT 10 years ago. Best recommendation for breast cancer prevention:

A. Annual MRI scanning of breast
B. Biennial mammography
C. Exemestane 25 mg daily
D. Tamoxifen 20 mg daily
E. Drink 1 glass of wine per day

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Clinical Review & Education

JAMA | US Preventive Services Task Force | RECOMMENDATION STATEMENT

Medication Use to Reduce Risk of Breast Cancer
US Preventive Services Task Force Recommendation Statement

US Preventive Services Task Force

USPSTF Breast CA Risk Reduction--Bkg

- 1:8 women develop breast CA
- #2 Cause of CA death in women
- 266,120 cases and 40,920 deaths 2018
- Need for preventive rx clear
- Lifestyle modifications: activity, weight, EtOH—limited data
- MRI in very dense breast (DENSE trial 11/19)

USPSTF Breast CA Reduction: Risk Calculators

- bcrisktool.cancer.gov
  - Hx dcis/lcis
  - Previous biopsies
  - Age
  - FH
  - Menarche
  - Menopause
- Breast Cancer Surveillance Consortium Risk Calc—App Store
  - Age
  - Race
  - FH
  - Hx Breast Biopsy
  - Bi-RADS breast density
- Our patient; risk = 4.13% at 5 years----average = 1.8%

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USPSTF Breast CA Risk Reduction-Findings

Table. Benefits and Harms of Risk-Reducing Medications Estimated From Meta-analysis of Randomized, Placebo-Controlled Trials[a,b]

Per 1000/5yrs

Outcome	Tamoxifen	Raloxifene	Aromatase Inhibitors
Benefits: Events Reduced (95% CI)[c]			
Breast cancer			
Invasive	7 (4-12)	9 (3-15)	16 (8-24)
ER+	8 (4-13)	8 (4-13)	15 (8-20)
ER−	ND	ND	ND
Noninvasive	ND	ND	ND
Mortality			
Breast cancer	ND	NR	NR
All-cause	ND	ND	ND
Fracture			
Vertebral	ND	7 (5-9)	ND
Nonvertebral	3 (0.2-5)	ND	ND
Harms: Events Increased (95% CI)[c]			
Vascular			
Venous thromboembolic event	5 (2-9)	7 (0.3-17)	ND
Deep vein thrombosis	ND	ND	NR
Pulmonary embolism	ND	ND	NR
Coronary heart disease events	ND	ND	ND
Other			
Endometrial cancer	4 (1-8)	ND	ND
Cataracts	26 (5-50)[d]	ND	ND

Abbreviations: ER−, estrogen receptor–negative; ER+, estrogen receptor–positive; ND, no difference; NR, not reported.

[a] See Nelson et al.[3,4]

[b] Trials included women whose 5-year risk of breast cancer may have been lower than 3%.

[c] Per 1000 women over 5 years of use.

[d] Results from the National Surgical Adjuvant Breast and Bowel Project Study of Tamoxifen and Raloxifene (STAR) trial.

Figure 2. Clinical Summary: Medication Use to Reduce Risk of Breast Cancer

Population	Women aged ≥35 y at increased risk for breast cancer	Women aged ≥35 y not at increased risk for breast cancer
Recommendation	Offer to prescribe risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors Grade: B	Do not routinely use risk-reducing medications, such as tamoxifen, raloxifene, or aromatase inhibitors Grade: D

Risk Assessment	Various methods are available to identify women at increased risk for breast cancer, including formal clinical risk assessment tools or assessing breast cancer risk factors without using a formal tool. The USPSTF does not endorse any particular risk-prediction tool. The National Cancer Institute Breast Cancer Risk Assessment Tool and the Breast Cancer Surveillance Consortium Risk Calculator are based on models tested in US populations and are publicly available. There is no single cutoff for defining increased risk for all women. Alternatively, clinicians may use combinations of risk factors to identify women at increased risk. Some examples of combinations of multiple risk factors in women at increased risk include (but are not limited to): age 65 years or older with 1 first-degree relative with breast cancer; age 45 years or older with more than 1 first-degree relative with breast cancer or 1 first-degree relative who developed breast cancer before age 50 years; age 40 years or older with a first-degree relative with bilateral breast cancer; presence of atypical ductal or lobular hyperplasia or lobular carcinoma in situ on a prior biopsy. When considering prescribing breast cancer risk-reducing medications, the potential benefit of risk reduction of breast cancer must be balanced against the potential harms of adverse medication effects.
Risk-Reducing Medications	Tamoxifen, raloxifene, and aromatase inhibitors all reduce primary breast cancer risk in postmenopausal women. Use of raloxifene and aromatase inhibitors is indicated only in postmenopausal women; only tamoxifen is indicated for risk reduction of primary breast cancer in premenopausal women.
Relevant USPSTF Recommendations	The USPSTF has made recommendations on screening for breast cancer and for risk assessment, genetic counseling, and genetic testing for *BRCA* genetic mutations.

For a summary of the evidence systematically reviewed in making this recommendation, the full recommendation statement, and supporting documents, please go to https://www.uspreventiveservicestaskforce.org.

USPSTF Breast CA Risk Reduction--Summary

- Assess breast CA risk in post-menopausal women with calculator from NIH or App Store
- > 3% 5-year risk is general threshold to consider prophylaxis
- Consider
  - Tamoxifen 20 mg/d x 5 years
  - Raloxifene 60 mg/d x 5 years
  - Exemestane 25 mg/d x 5 years
  - Anastrazole 1 mg/d x 5 years
- Tamoxifen & Ralox → > VTE
- Tamox & Ralox → < osteoporotic fx
- Tamox → endometrial CA and cataracts
- AI → myalgias
- All→ VM symptoms

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Baloxavir Marboxil for Prophylaxis against Influenza in Household Contacts

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Baloxivir Prophylaxis Background

- Household contact common source of influenza transmission
- High risk: > 65, post-partum, SNF, asthma, severe neuro disorders, CVD, sickle cell, DM, immunosuppression, kidney/liver disease.
- Vax is mainstay of prophyx
- Neuraminidase inhibitors effective—indicted for 1 week post exposure.
- Baloxivir = endonuclease inhibitor approved 2018 Influenza A/B.
- Multicenter 2x-blind, randomized, placebo controlled post-exposure prophylaxis after exposure to confirmed + household contact in Japan—single dose
- 749 randomized—innoculum unclear.

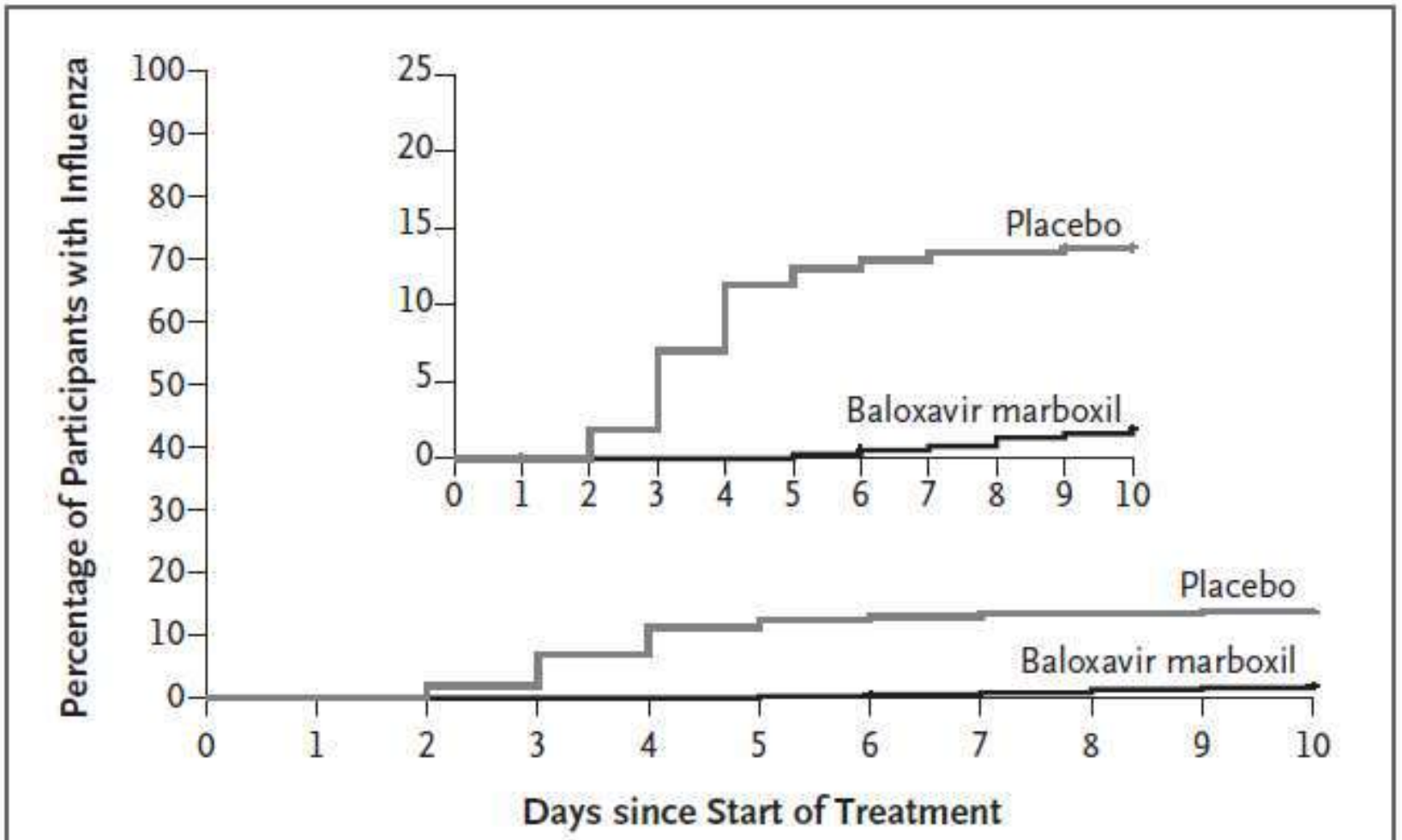

Figure 1. Cumulative Percentage of Participants with Clinical Influenza in the Modified Intention-to-Treat Population.

Table 2. Primary and Secondary End Points (Modified Intention-to-Treat Population).*

End Point	Baloxavir Marboxil (N=374)		Placebo (N=375)		Adjusted Risk Ratio (95% CI)
	Participants with End Point	Percentage (95% CI)	Participants with End Point	Percentage (95% CI)	
	no./total no.		*no./total no.*		
Primary end point: laboratory-confirmed clinical influenza†					
In the modified intention-to-treat population	7/374	1.9 (0.8–3.8)	51/375	13.6 (10.3–17.5)	0.14 (0.06–0.30)‡
Among those who had a negative RT-PCR result at baseline and contact with a RT-PCR–positive index patient	5/344	1.5 (0.5–3.4)	39/337	11.6 (8.4–15.5)	0.13 (0.05–0.31)
Among those <12 yr of age	3/71	4.2 (0.9–11.9)	11/71	15.5 (8.0–26.0)	0.27 (0.08–0.90)
Among those ≥12 yr of age	4/303	1.3 (0.4–3.3)	40/304	13.2 (9.6–17.5)	0.10 (0.04–0.28)
Among those with underlying high-risk factors	1/46	2.2 (0.1–11.5)	8/52	15.4 (6.9–28.1)	0.13 (0.02–0.94)
Secondary end points					
RT-PCR–confirmed influenza virus infection regardless of fever and symptoms	49/374	13.1 (9.9–16.9)	114/375	30.4 (25.8–35.3)	0.43 (0.32–0.58)
RT-PCR–confirmed illness§	20/374	5.3 (3.3–8.1)	84/375	22.4 (18.3–27.0)	0.24 (0.15–0.38)
RT-PCR– or seroconversion-confirmed influenza virus infection regardless of fever and symptoms¶	59/374	15.8 (12.2–19.9)	119/375	31.7 (27.0–36.7)	0.50 (0.38–0.66)
RT-PCR– or seroconversion-confirmed illness‖	23/374	6.1 (3.9–9.1)	86/375	22.9 (18.8–27.5)	0.27 (0.17–0.42)
Asymptomatic infection confirmed by RT-PCR assay or seroconversion**	14/374	3.7 (2.1–6.2)	13/375	3.5 (1.9–5.9)	1.08 (0.52–2.27)

Baloxivir Prophylaxis Conclusions & Limitations

- RRR for PCR confirmed influenza illness after household exposure = 87%
  - ARR = 10.1 → NNT = 9.9
- RRR for PCR/Serology confirmed illness = 73%
  - ARR = 16.8 →NNT = 5.9
- 72% received Baloxivir w/i 24^0 onset of illness of index
- Only 3.6% > 65 yo
- No major SE difference
- Single dose Baloxivir in household contact → dramatic reduction in influenza risk.
- Vaccine #1….very high risk household contacts → Baloxivir 1 dose.

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2020 Primary Care Update Summary

- START: Mild Persistent Asthma—prn budesonide/fomoterol superior to daily maintenance
- PACE: CRP helps guide Abx decision on COPD exacerbation
- VITAL: Minimal Fish Oil benefit in general pop—no CA benefit
- REDUCE-IT: 2^{o} prevention with > TG via high dose enriched EPA
- POSA: Undiagnosed OSA common and major surgical risk
- USPSTF Breast Cancer Prevention with SERM or AI
- Baloxivir effective in post-exposure prophylaxis

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