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Disclosure

Speaker name:

LEDERLE

- ☐ I have the following potential conflicts of interest to report:
 - ☐ Consulting
 - ☐ Employment in industry
 - ☐ Shareholder in a healthcare company
 - ☐ Owner of a healthcare company
 - ☐ Other(s)
- ☒ I do not have any potential conflict of interest

VIEWPOINT

Does Abdominal Aortic Aneurysm Screening Save Lives?

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This Viewpoint is about the upper boundary of a 95% confidence interval, specifically the one around the reduction in total mortality observed in meta-analyses of randomized trials of ultrasound screening for abdominal aortic aneurysm (AAA) in men older than 65 years. Four such trials involving more than 100 000 men have

The potential impact of this distinction on screening practice and policy is evident in 2 prominent articles published in 2015 that challenged the value of ultrasound screening for AAA. Both emphasized what their authors perceived as a lack of a demonstrated reduction in total mortality from screening. Surprisingly, the

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Death, significance, and AAA screening

- 4 RCTs of US screening for AAA in men >65 yo
- 50% ↓ in AAA-related mortality
- AAA caused 3% of all deaths
- So 1.5% ↓ in total mortality expected, ... and found
- But is it “statistically significant”?
- Hairsplitting, but this is how the question “Does AAA screening save lives?” is being addressed!

Choice of primary outcome

- Screening trials of fatal diseases have always used disease-specific mortality as their primary outcome
- A reduction in disease-specific mortality is accepted by most authorities as proof of benefit
- In 2002, Black & Welch argued that deaths indirectly caused by screening might not be identified as such, leading to a false conclusion of benefit

Why not use total mortality?

- Feasibility, not preference
- At 10 yrs, MASS had 30% total mortality.
- To detect 1.5%↓ (2-sided $\alpha=.05$, 80% power) would require 325,000 randomized & followed 10 yrs (5x actual size of trial).
- Even meta-analyses of the longest follow-up of all trials of a screening test lack sufficient power
- But, reductions in total mortality are occasionally observed in large screening trials (NLST, MASS)

Why it matters

- In 2015, two prominent articles stressed the importance of total (vs disease-specific) mortality
- Both challenged the value of AAA screening
- Both emphasized a perceived lack of a reduction in total mortality from screening
- But both got the numbers wrong!

Article #1

Does screening for disease save lives in asymptomatic adults?

Saquin & Ioannidis, Int J Epi 1/15

- Set out to examine all RCTs & meta-analyses of screening tests for cancer & CV dis, including AAA
- Concluded: a ↓ in total mortality “has not been documented in the **latest available** meta-analysis of multiple trials for **any** of the examined topics”.
- Message that “screening does not save lives” amplified in 3 accompanying commentaries (and in BMJ, JAMA, Gupta Guide, etc)

Why so much attention to an article in Int J Epi?

BMJ CONFIDENTIAL

John Ioannidis: Uncompromising gentle maniac



Biography

John Ioannidis, 50, is the scourge of sloppy science, whose 2005 paper, Why Most Published Research Findings are False, has achieved near legendary status. He was still hissing excitement as he wrote nos, an island in the Cyclades,

Five minutes with . . . John Ioannidis

The Stanford University professor talks about the problems with meta-analyses

Susan Mayor

London

BMJ 2016;354:i5184 doi: 10.1136/bmj.i5184 (Published 28 September 2016)

Cited > 2100 times

Sloppy Science

- They dodged the 2 large screening trials that reported ↓ total mortality from screening
- National Lung Screening Trial: excluded because controls got chest x-rays (2° PLCO, → ↑ difficulty)
- Cited 2012 MASS report, but not in meta-analysis
- Used 2010 Takagi meta-analysis that preceded it
- They neither updated it themselves, nor found (in their 2014 search!) the 2012 Takagi update that included MASS (and reported ↓ in total mortality)
- Got wrong conclusion due to inadequate search

Article #2

Estimating overdiagnosis in screening for AAA

Johansson BMJ 2015

- AAA screening should be “revisited”, in part because “there was no significant reduction in overall mortality”, citing 2014 USPSTF review (the TF didn’t ? screening)
- USPSTF total mortality, random effects models:
 - ‘longest f/u’ of all 4 RCTs: RR 0.99 (0.97, 1.00) “NS”
 - by yrs, longest = 13-15y (3 RCTs): 0.98 (0.97, 1.00) “NS”
- We calculated p values (USPSTF didn’t!): 0.033 & 0.042
- USPSTF authors rounded .999 to 1.00 in each case (!)
- Takagi 2012 meta-analysis: to 3 decimal places

Statistical Reviewer for Journal #3 (of 4) on how I must have misunderstood

“No one uses the upper end of a confidence interval to compute a p-value. It seems very unlikely that any previous authors would have made the mistake of using the rounded-off upper confidence interval as the basis for determining the significance of an effect.”

(Unfortunately, (s)he didn't bother to check the USPSTF article)

Correction: Ultrasonography Screening for Abdominal Aortic Aneurysms

TO THE EDITOR: In our article, "Ultrasound Screening for Abdominal Aortic Aneurysms: A Systematic Evidence Review for

(1° analysis)

The DerSimonian–Laird random-effects models for all-cause mortality at either 13 to 15 years or longest follow-up do not cross 1.00 at the upper 95% CI bound (RR, 0.986 [CI, 0.972 to 0.999]); however, after rounding to 2 significant digits we concluded a lack of statistical significance at this longest time point.

Although we stand by our rounding approach, we acknowledge that different approaches could lead people to somewhat different conclusions, particularly if one adheres to conventional indicators of statistical significance as their primary focus.

However, a careful reader, Frank Lederle,

So Johansson got it wrong by believing the USPSTF reviewers, who got it wrong by rounding

Long-term Outcomes of the Western Australian Trial of Screening for Abdominal Aortic Aneurysms

Secondary Analysis of a Randomized Clinical Trial

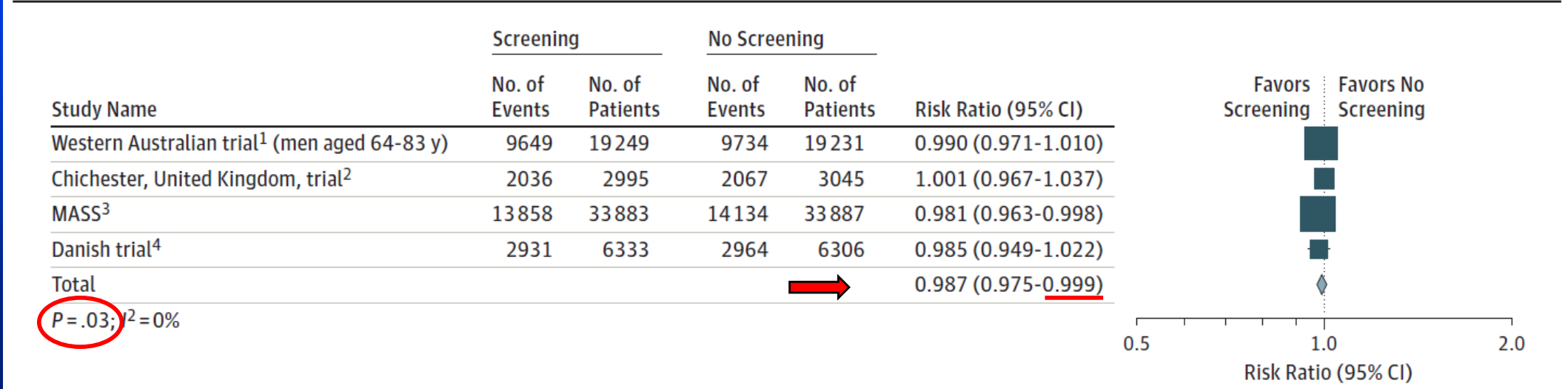
JAMA Internal Medicine December 2016 Volume 176, Number 12 1767

Invited Commentary

The Last (Randomized) Word on Screening for Abdominal Aortic Aneurysms

Frank A. Lederle, MD

Figure. Random-Effects Model for Meta-analysis of All-Cause Mortality at Longest Reported Follow-up in the 4 Trials of Abdominal Aortic Aneurysm Screening



Déjà vu

Multiple meta-analyses got it wrong *before* 2012
MASS report, incorrectly saying ↓ total mortality was significant
(due to a problem with randomization in WA trial)

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Other meta-analysts have made the same error of using unadjusted deaths from the West Australia trial, including Cosford in a Cochrane review⁵ and Takagi on multiple occasions,^{6–9} so it is time to set the record straight.

Response to comment on “Screening for abdominal aortic aneurysm and overall mortality in men”

As a response to the meta-analysis: “Screening for abdominal aortic aneurysm reduces overall mortality in men. A meta-analysis of the mid- and long-term effects of screening for abdominal aortic aneurysms”, we are grateful for Professor Lederle’s insightful observation that the significant finding concerning overall mortality was caused by an age imbalance in the West Australian (WA) study. Due to a problem in the first year of randomisation (1996), there were indeed more old men in the control group of this study, and consequently more deaths. The optimal way to clarify this would be a merged dataset allowing proper survival analysis with

The flap of a butterfly wing can change the climate (Lorenz 1972)

- Total mortality from AAA screening was not significantly ↓ before 2012 MASS, but is after it
- In both cases, this is despite multiple published meta-analyses concluding the contrary
- With 2012 MASS included, it can no longer be said that “AAA screening does not save lives”
- Debate on AAA screening will surely continue, but first we should get the numbers right