Università degli Studi di Padova
Dipartimento di Scienze Cardiologiche Toraciche Vascolari
Unità di Igiene e Sanità Pubblica
Laboratorio di Valutazione dei
Servizi Sanitari e della Promozione della Salute

Screening di Popolazione

*Where are we now and what's next_*

14.00 Saluti e presentazione

Vincenzo Baldo
Università degli Studi di Padova

14.10 Programmi di screening negli Stati Uniti: where are we now and what's next?

Mark H. Ebell
University of Georgia, US Preventive Services Task Force

15.00 Programmi di screening in Italia: where are we now and what's next?

Marco Zappa
Valutazione Screening e Osservatorio Nazionale Screening
Istituto per lo studio e la prevenzione oncologica, Regione Toscana

15.30 Programmi di Screening in Veneto: where are we now and what's next?

Adriana Montaguti
Coordinamento Regionale Screening Oncologici
Direzione Prevenzione, Sicurezza Alimentare, Veterinaria, Regione Veneto

16.00 Screening cardiovascolare: esperienze regionali a confronto

Federica Michieletto
Direzione Prevenzione, Sicurezza Alimentare, Veterinaria, Regione Veneto

Mara Morini
già Direttore Cure Primarie AUSL Bologna

Grazia Orizio
Dipartimento Cure Primarie ATS Brescia

16.30 Conclusioni

Manuel Zorzi
Registro dei Tumori del Veneto Regione Veneto

Alessandra Buja
Università degli Studi di Padova

Giovedì 18 maggio 2017
ore 14.00

Aula A - Istituto di Igiene
via Loredan 18 — Padova

Segreteria organizzativa ed informazioni:
Alessandra Buja - alessandra.buja@unipd.it
Mirko Claus - mirko.claus@studenti.unipd.it

UNIVERSITÀ DEGLI STUDI DI PADOVA

DIPARTIMENTO DI SCIENZE CARDIOLOGICHE TORACICHE E VASCOLARI

UNITÀ DI IGIENE E SANITÀ PUBBLICA
LABORATORIO DI VALUTAZIONE DEI SERVIZI SANITARI E DELLA PROMOZIONE DELLA SALUTE

The United States Preventive Services Task Force: how we make guidelines, and update on new recommendations

Mark H. Ebell MD, MS

Professor, University of Georgia

Member of the USPSTF: 2012-2015

Consultant to USPSTF: 2016 - present

Disclosure

Dr. Ebell served as a member of the USPSTF from January, 2012 till December, 2015. He currently serves as a consultant to the American Institutes for Research, providing guidance regarding how public comments are handled. His comments, statements, and opinions are his alone, and do not represent the official views of the USPSTF, the United States government, American Institutes for Research, or the University of Georgia.

A brief biosketch

- University of Michigan: MD 1987, Family Medicine residency 1990, and MS Public Health 1994
- Professor, College of Public Health, University of Georgia
- Research interests: evidence-based practice, meta-analysis of diagnosis, decision support systems, clinical decision rules, acute respiratory infections, primary care.
- **Relevant for today: member US Preventive Services Task Force 2012-15**

Today's topics

1. The USPSTF and its processes (20 min)
   Domande? (5)
2. The challenges of screening (10 min)
   Domande? (5)
3. Recent cancer screening recommendations: colorectal, breast, and prostate (20 min)
   Domande? (5)
4. Cardiovascular prevention: aspirin and statins (20 min)
   Domande? (5)

1. The USPSTF and its processes

Why would we want national guidelines for screening and prevention?

The argument for guidelines

- Summarize the best available evidence

  in order to…
- Reduce inappropriate variation in care

  and…
- Provide regular updates to the guidance

Especially important for screening and preventive services, where the population is asymptomatic, and overscreening, overdiagnosis, and overtreatment are potential problems

What is the USPSTF?

Established in 1984, makes recommendations on over 70 conditions:

- Screening in asymptomatic persons
- Primary prevention (counseling, medications)

Service must be performed by **primary care physician** or referable from primary care office

USPSTF does not consider financial impact of recommendations (but should it?)

Who is on the USPSTF?

- Independent panel of 16 unpaid experts in primary care medicine: family medicine (“GP”), pediatrics, obstetrics/gynecology, nursing
- Carefully checked for financial conflict of interest
- Serve 4 year terms as volunteers: 3 meetings per year + many phone calls + much reading and study.
- Approximately 10% of effort for a year.

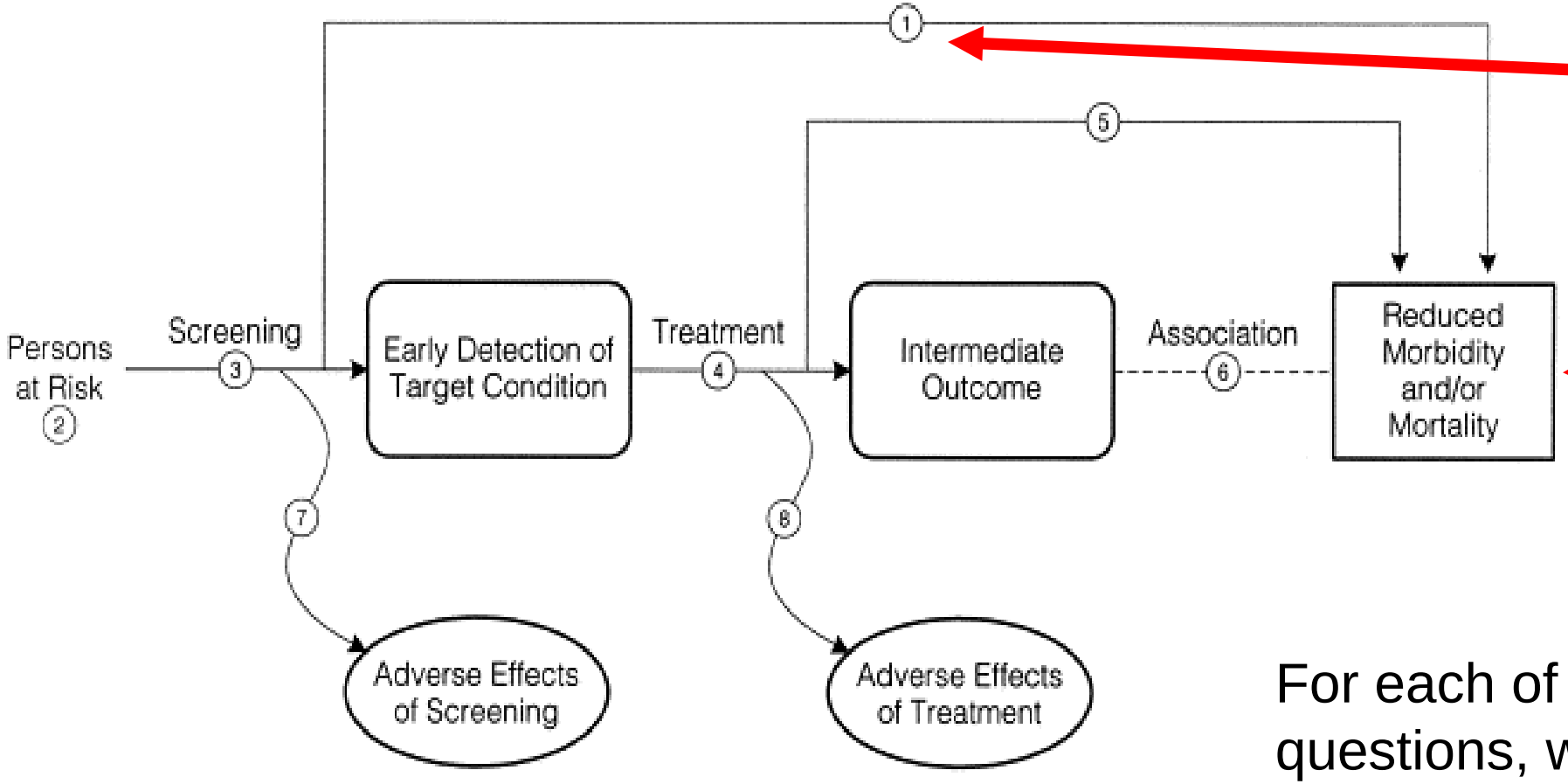
The USPSTF Process

Institute of Medicine recommends the USPSTF as a model for guideline development:

- Recommendations based on systematic reviews of the best available evidence
- Considers benefits and harms, as well as certainty
- Free of conflict of interest
- Methods are transparent
- Obtains public input and input from expert peer reviewers
- Regularly updated (~ every 5 years)

Step 1. Develop a Research Plan

The analytic framework guides which evidence we seek



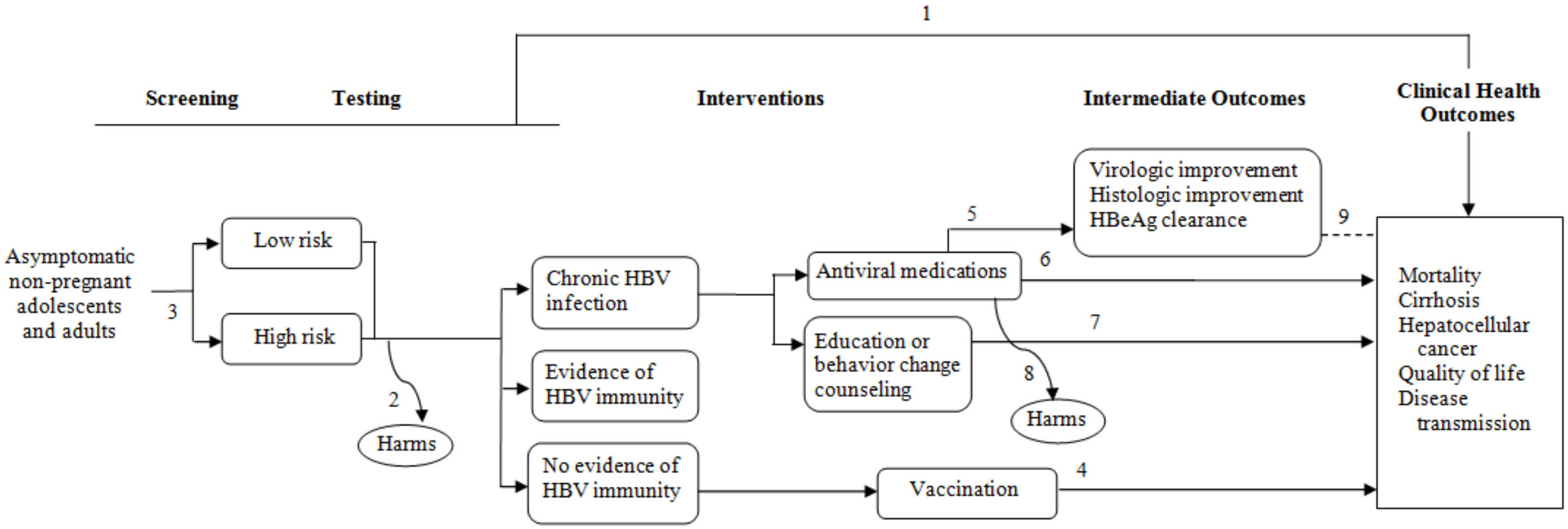
Direct evidence pathway

Indirect evidence pathway

For each of the numbered key questions, we will gather the best available evidence.

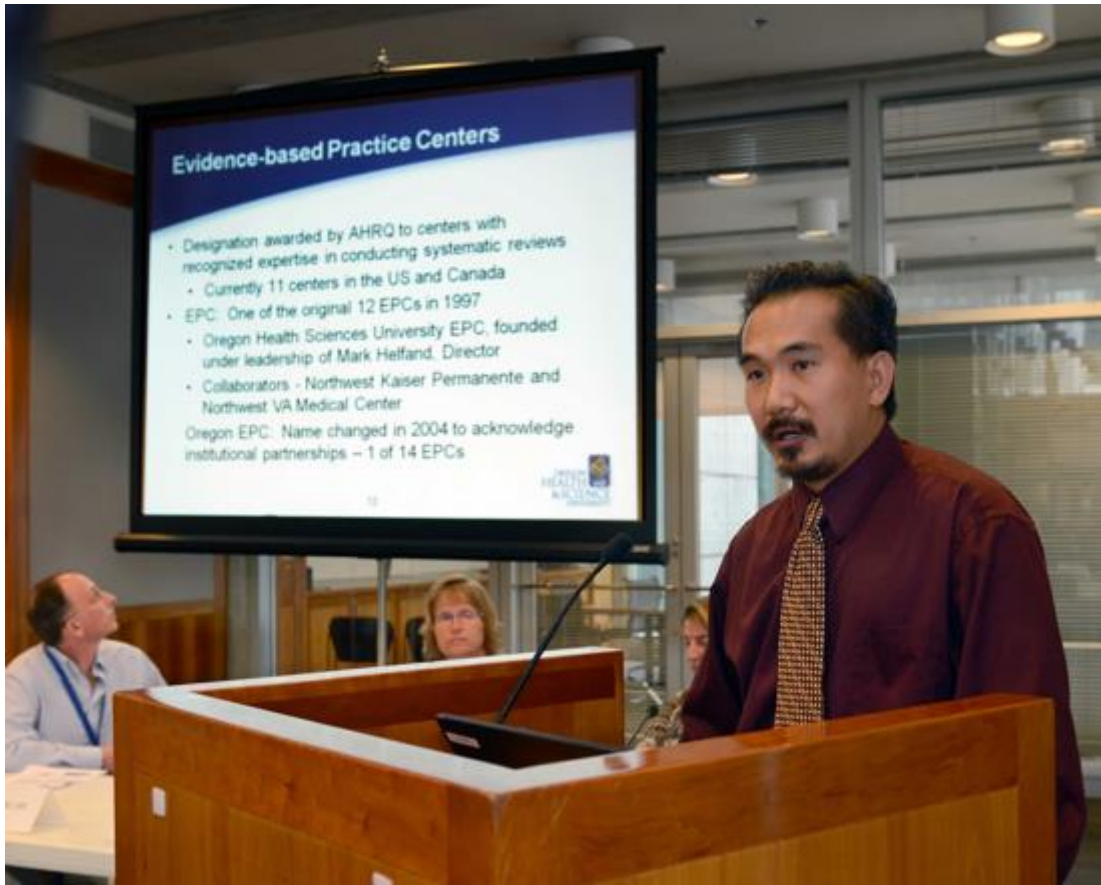
Sample analytic framework: Hep B Screening

Each number is a key question that must be answered with the best available evidence.



Step 2. Develop a draft evidence report to answer each of the key questions

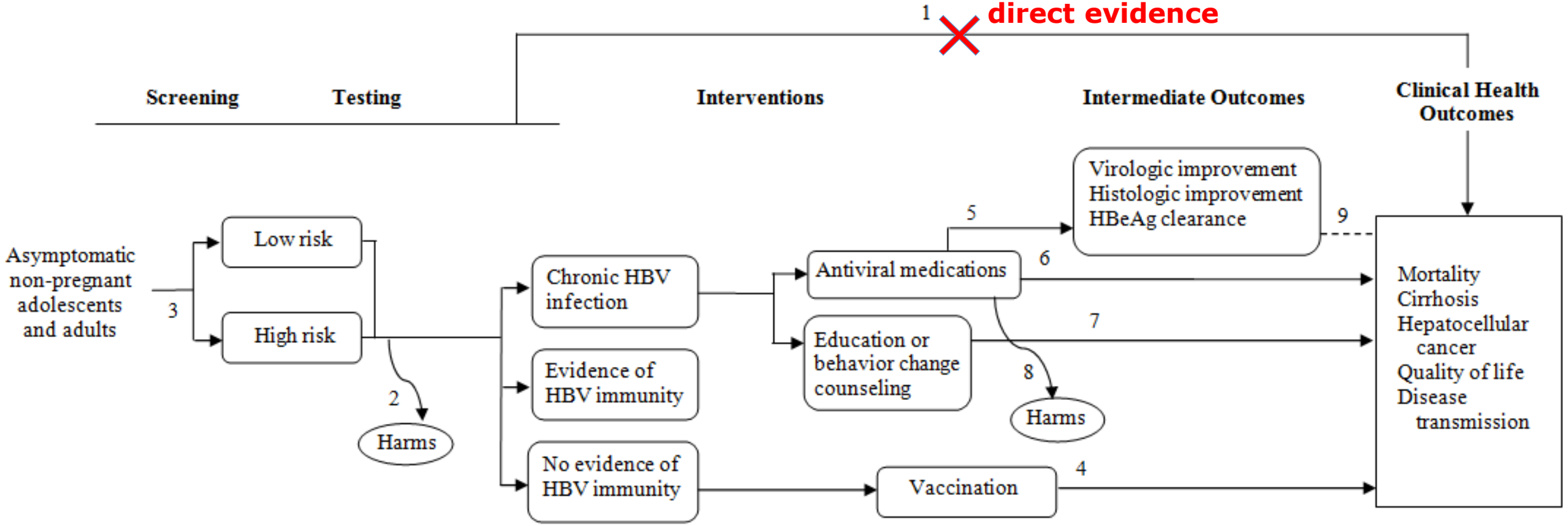
- Performed by federally funded “Evidence-Based Practice Centers”
- Team of clinicians and experts in evidence synthesis
- Steps (6 – 12 months)
  - Define and retrieve **all** relevant evidence
  - Evaluate the quality of individual studies (Good, Fair or ~~Poor~~)
  - Synthesize the results if possible (meta-analysis)
  - Judge the strength of available evidence for each key question



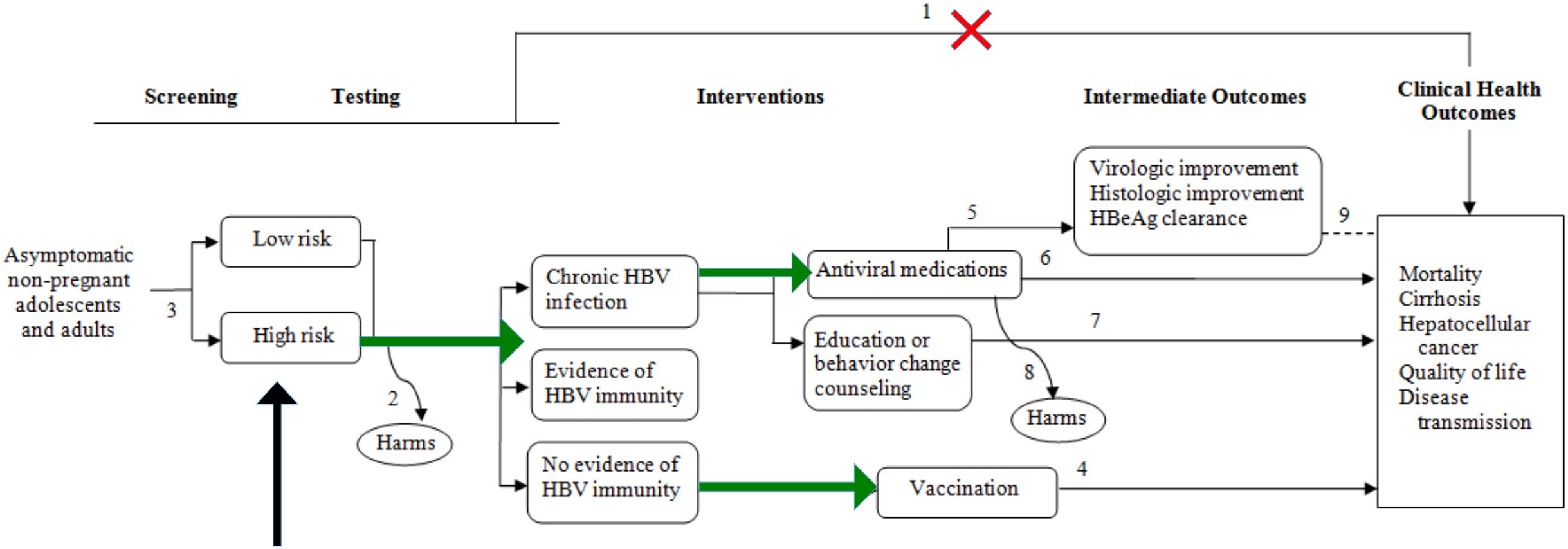
Sample analytic framework: Hep B Screening

Key Question 1: Is there direct evidence of improved health outcomes from RCT's?

In this case, no direct evidence

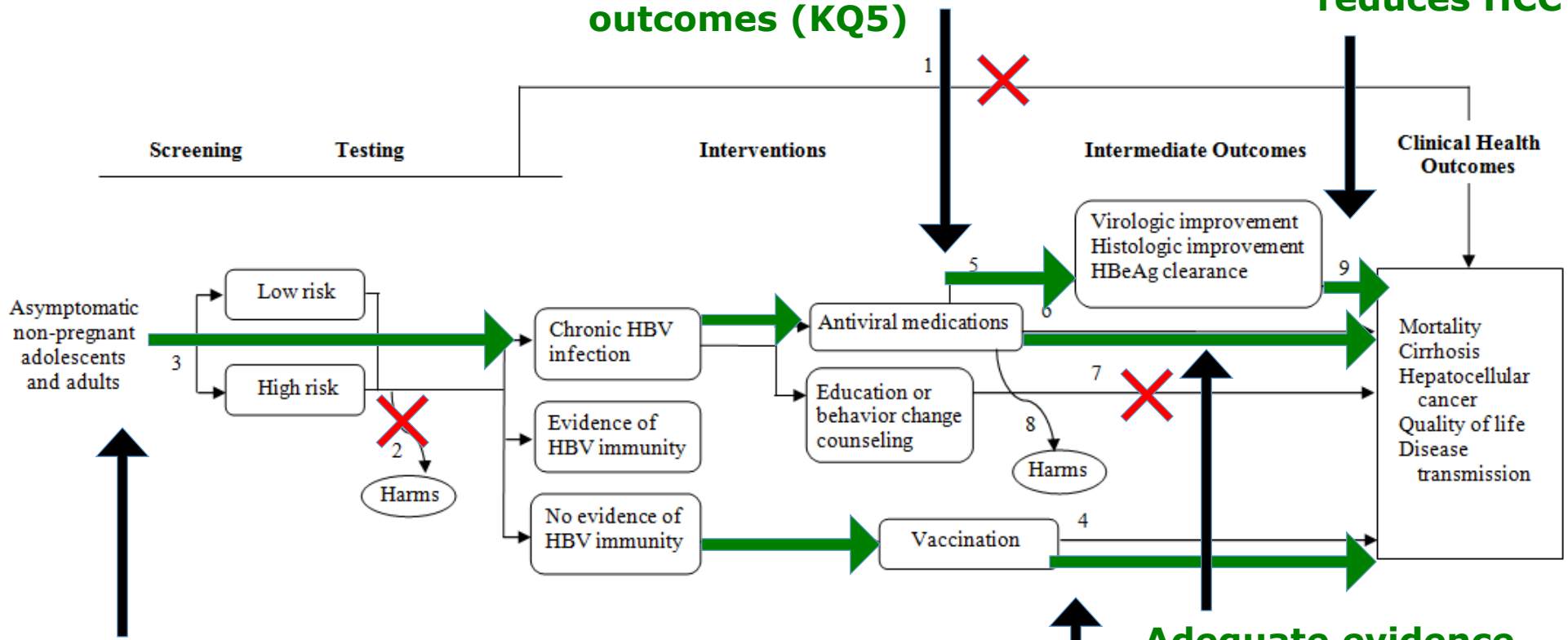


Sample analytic framework: Hep B Screening



Adequate evidence that we can identify high risk groups based on single risk factors (KQ3).

Sample analytic framework: Hep B Screening



Convincing evidence tx improves intermediate outcomes (KQ5)

Adequate that improving intermediate reduces HCC (KQ9)

Adequate evidence that we can identify high risk groups based on single risk factors (KQ3).

Adequate evidence that vaccination prevents disease acquisition (KQ4).

Adequate evidence that antivirals reduce HCC (KQ6).

Step 3. Develop a draft recommendation

- Focus is on net benefit

Net Benefit = Benefit - Harm

- Based on the evidence summary, for each key question:
  - How ***certain*** are we about the benefits and harms?
  - What is the ***magnitude (size)*** of both benefits and harms?

Step 5. Assign a grade to the recommendation

	Magnitude of Net Benefit			
Certainty of Net Benefit	**Substantial**	**Moderate**	**Small**	**Zero/negative**
High	**A**	**B**	**C**	**D**
Moderate	**B**	**B**	**C**	**D**
Low	**Insufficient (I Statement)**			

Step 4. Post draft recommendation for public comment

- Vary widely in number, content
- Who comments: stakeholder organizations, experts, researchers, disease survivors, and individual citizens,
- Some are much more useful than others!

#: 16 *Role: Consumer or patient* *Organization: Ms.*

ID: 10568

Comment

Based on the evidence presented in this draft Recommendation Statement, do you believe that the USPSTF came to the right conclusions? Please provide additional evidence or viewpoints that you think should have been considered.

NO

ONE MORE TIME you deny needed services and people will die from your denial of services

Do you have other comments on this draft Recommendation Statement?

You formally and presently cointinually deny medical services and as it gets worse and worse, my family and friends are becoming sick and/or sicker and it is due to your denials of services.

You should have a conscience.

Step 5. Create Final Recommendation

- Review public comments
- Discuss, and discuss some more
- Write final recommendation statement
- Yes, it changes sometimes

- Disseminate

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New Guidelines on Breast Cancer Draw Opposition

By RONI CARYN RABIN
Published: November 16, 2009

Karen Young-Levi has gone for a mammogram every year since she turned 40, and she would not skip the procedure any more than she would skip her spin classes at the gym or stop wearing her seat belt. "It's my security blanket," said Ms. Young-Levi, 43, of Medford, N.J.

Enlarge This Image

Sabina Louise Pierce for The New York

So Ms. Young-Levi was confused and unnerved last week when news seeped out about new federal recommendations to scale back routine breast cancer screening. Like many women, she reacted with dismay and disbelief that the value of the one screening test she relied on had been questioned.

"If someone ran a computer analysis that determined that

Done

So, everyone must like the USPSTF.

Right?

THE WALL STREET JOURNAL. | OPINION

OPINION | May 25, 2012, 12:56 p.m. ET

Prostate Testing and the Death Panel

A free economy leads to life-saving innovations. A highly taxed and overregulate leads to government agencies that discourage their use.

By TOM PERKINS

A recent announcement by the U.S. Preventative Health Service can rather simply be summed up: Most men eventually get prostate cancer, but most don't die from it; those who do are mostly over 75 years of age, so that ends their continuing burden on the public purse. Further, early and prolonged testing is expensive, and can lead to medical complications from biopsy examination.

Happily I can report that I have successfully completed my 80th trip around the sun. A few years ago prostate cancer was detected by my annual prostate-specific antigen (PSA) test; it was of a particularly aggressive type, as revealed by a routine biopsy.

That test led to surgery, radiation and hormone therapy.

Unfortunately, the cancer returned, and for the last couple of years I have been undergoing both routine and quite advanced experimental therapies, and everything has been monitored and controlled by PSA tests. Happily, the cancer has been knocked

DCPatient An Impatient Patient's Perspective on Health Care Today blogged live from Washington DC

The Real Death Panel: USPSTF and Breast Cancer

November 17th, 2009 by DCPatient Leave a reply »

Tweet

In today's Annals of Internal Medicine and splashed across the front pages of many major newspapers are the shocking new recommendations of the U.S. Preventive Services Task Force (USPSTF) that:

1. Women should not begin routine mammograms until age 50 (instead of the current age 40)
2. Women should not be taught to do monthly self-examinations
3. Physician/clinical breast exams have insufficient evidence of benefit.

Was there a new study that changed their minds? No, just some computer modeling.

Did this modeling show that lives would be saved? No, annual mammography for all women beginning at age 40 reduced the death rate from breast cancer by 15%, yes, fifteen percent. According the American Cancer Society in 2009, among women younger than 45 – 6, 460 were diagnosed with in situ (confined to the breast) cancer; 18,640 had invasive breast cancer; and 2,820 died. These women and their families don't matter? Apparently mammography saving lives is not a persuasive argument for these folks.

The justification of the USPSTF and its supporters – false positive readings of earlier screening may cause anxiety and 33/1000 women may have an unnecessary biopsy.

Here’s what a Death Panel really looks like!

www.medscape.com/viewarticle/872599

Apps | Todo Online | American Family Ph... | Athens and local stuff | Bike touring | Learn how and w

News & Perspective

GOP Begins New Scrutiny of US Preventive Services Task Force

Alicia Ault

November 30, 2016

13

WASHINGTON — The United States Preventive Services Task Force (USPSTF) needs to be more accountable and transparent about how it makes its recommendations and should appoint specialists for membership, said Republican members of Congress at a hearing held here today.

The House Energy and Commerce Health Subcommittee convened on November 30 to discuss the USPSTF Transparency and Accountability Act of 2016, the latest iteration of legislation first proposed by Rep. Marsha Blackburn (R-Tenn) in 2015.

The proposal may now have a better chance of advancing, given that Republicans control the House and Senate and the White House.

No Democrats attended the hearing, as they were otherwise occupied in voting on their new leader in the House. But Democrat Bobby Rush of Illinois is a cosponsor of the new bill, which is still being drafted.

OK, not everyone!

AUA, others continue blitz on USPSTF reform

Proposed bill would require consultation with external experts

September 01, 2016 | By Bob Gatty

Bob Gatty

One of the top remaining federal issues for urologists as Congress heads into full campaign mode is the effort to reform a federal entity that can virtually dictate whether various procedures are covered by federal health programs and, ultimately, by private insurers.

That entity is the U.S. Preventive Services Task Force (USPSTF), which in May 2012 recommended against PSA-based screening for prostate cancer. It was a decision that drew the ire of the AUA and other organizations within the specialty and prompted an all-out blitz on Congress to reform the way the USPSTF does business.

Domande?

2. Some don’ts of screening

- Don’t confuse astronomy with biology
- Don’t use 5 year survival to evaluate screening programs
- Don’t forget that overdiagnosis is a major potential harm
- Don’t overscreen

Screening is difficult

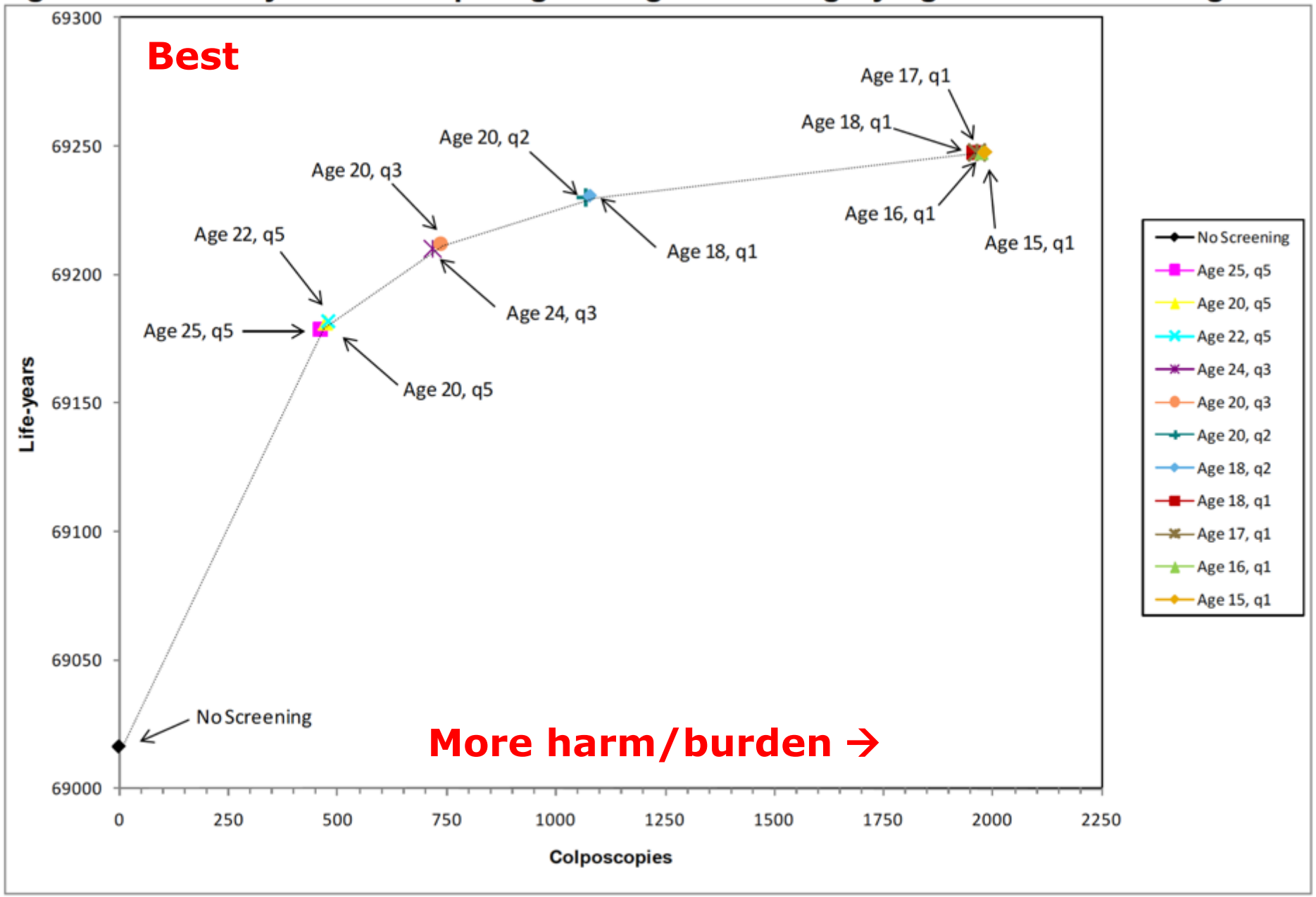
- Key point: we are doing something to a perfectly healthy, happy person.
- We have to be very certain that benefits clearly outweigh harms.
- Many potential harms:
  - Direct harm of intervention
  - Harm of downstream tests and biopsies
  - Cost
  - Worry
  - Most importantly overdiagnosis (detecting cancer that never would have caused any harm)

Biology ≠ astronomy

- Too often, astronomy is the basis for our screening intervals
- What if we lived on Mars?
- Increasingly, screening intervals are not annual

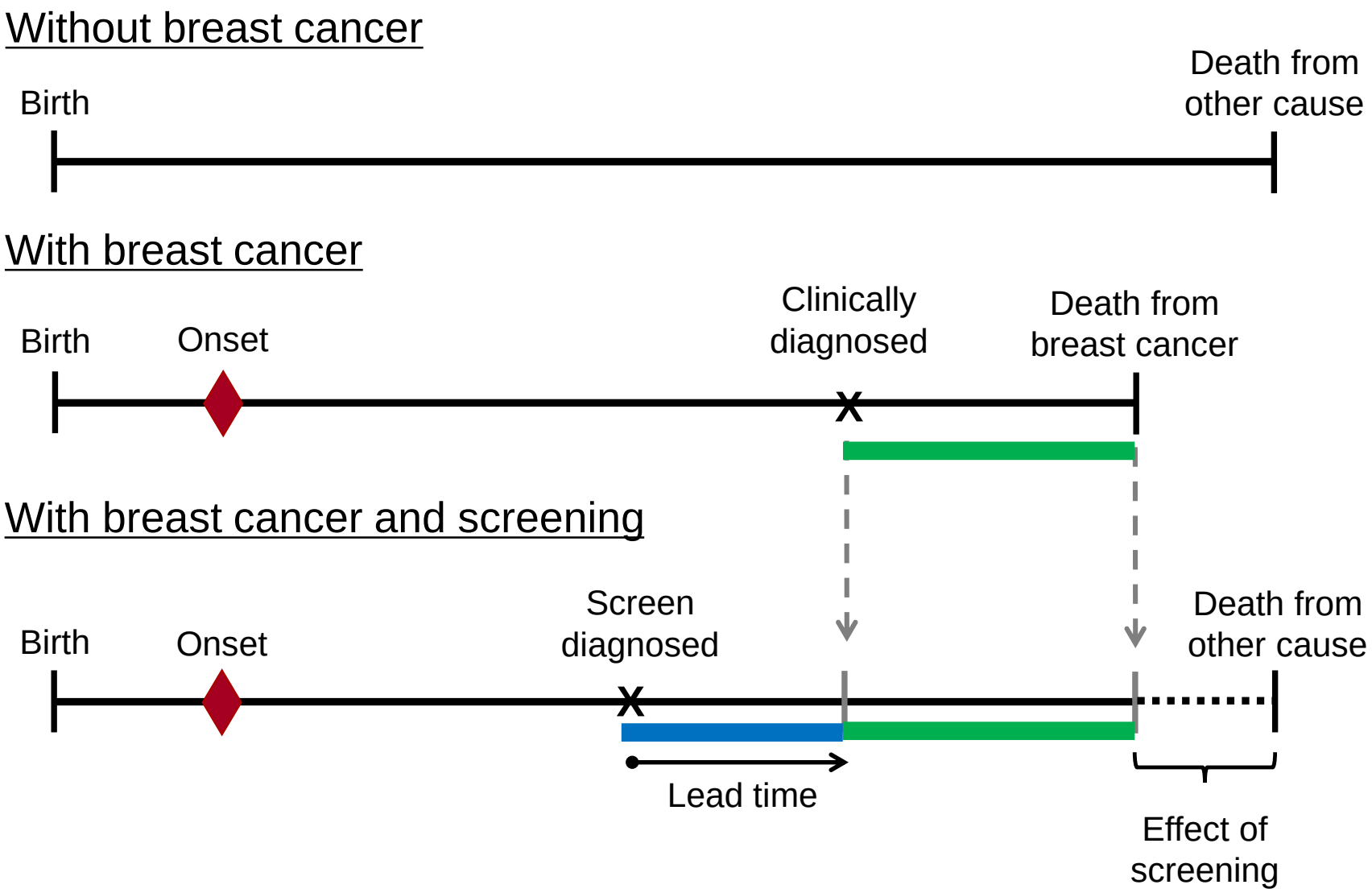
A year on:
Mercury: 88 days
Venus: 225 days
Mars: 687 days
Jupiter: 4343 days

Figure 2. Efficiency Curve Comparing Strategies Differing By Age at First Screening*



*Strategies presented are those identified as efficient using incremental colposcopies per life-year.

Don’t use 5 year survival to evaluate screening programs



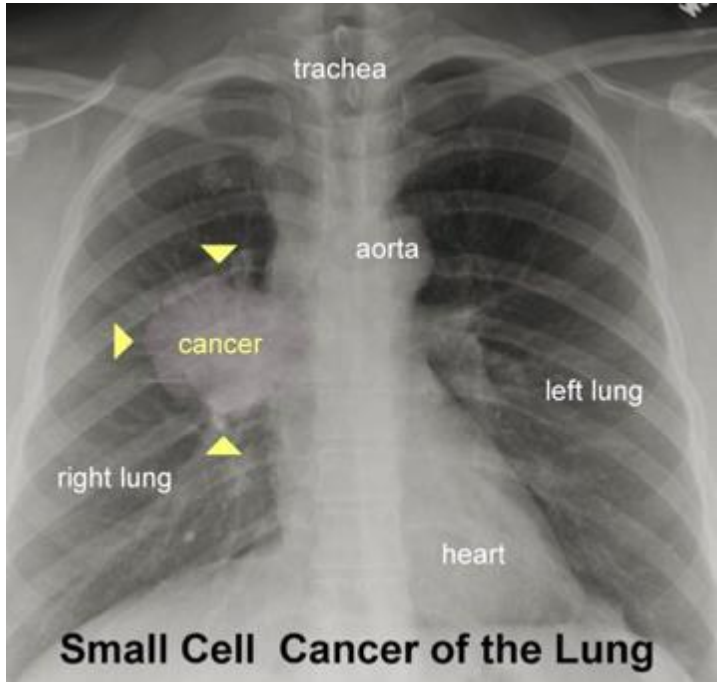
Survival from time of diagnosis ALWAYS increases with screening, as does % surviving 5 years from diagnosis (“5 year survival”)

However, mortality may be unchanged.

NEVER trust 5 year survival when evaluating screening programs

5 year survival vs mortality: Mayo Clinic Study of Lung Cancer Screening with CXR

- Randomized smokers to annual CXR or nothing
- 5 year survival for lung cancer:
  - Screened: 35%
  - Controls: 19%
- But…mortality rates due to lung cancer did not differ:
  - Screened: 4.4 deaths/1000 person-years
  - Controls: 3.9 deaths/1000 person-years



Source: JNCI 2000; 92:1308-16.

Overdiagnosis

- **Old thinking**: no cancer → precancerous lesion → asymptomatic cancer → symptomatic cancer → death

- **New thinking**: several possible paths
  - Cancer progresses, cause symptoms, then death
  - Progresses and causes clinical symptoms, but not death, and is treatable
  - Grows slowly but never causes any symptoms
  - Precancerous lesions that regresses

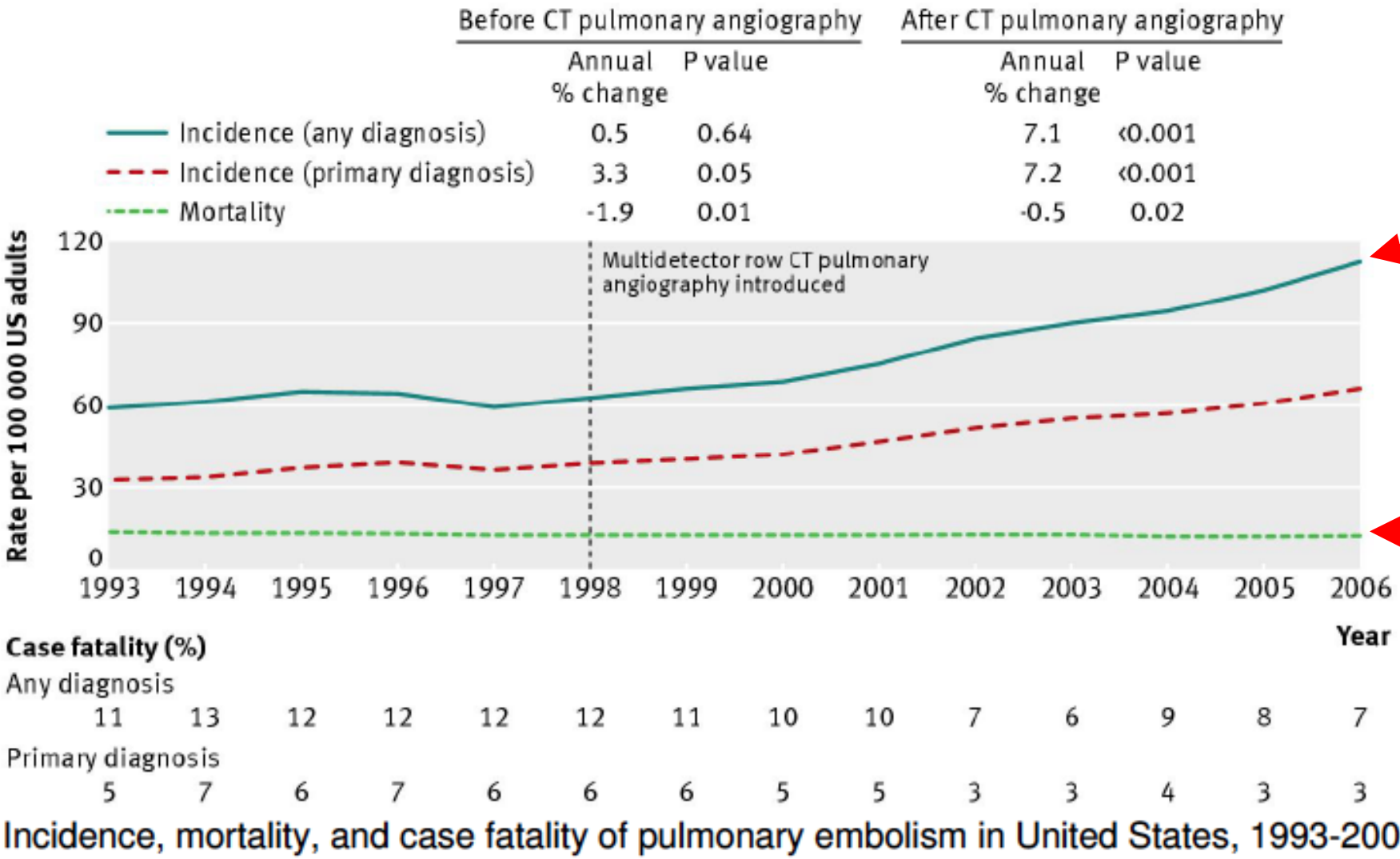
Types of overdiagnosis: Tumor – Patient Classification

Tumor A: Asymptomatic malignant disease that regresses spontaneously if left alone (neuroblastoma)

Tumor B: Asymptomatic malignant disease that either stagnates or progresses too slowly to be life threatening in even the longest of lifetimes (prostate cancer)

Patient: Asymptomatic malignant disease that progresses quickly enough to be life threatening during a lifetime of typical length, but death because of another cause occurs prior to what would have been the destined date of symptomatic diagnosis had screening not occurred (lung cancer)

Not just cancer: pulmonary emboli incidence and mortality from 1993 to 2006



Incidence, mortality, and case fatality of pulmonary embolism in United States, 1993-2006.[26]

Incidence rising with new CT technology

Mortality essentially unchanged

Examples of overscreening in United States

- Among elderly women with advanced dementia, 20% have mammograms
- Among patients with advanced cancer unlikely to live more than a year or two
  - Mammography: 9%
  - Pap test: 6%
  - PSA test: 15%
  - Colonoscopy: 2%
- May be partially motivated by market-based health system in US.

Source: Am J Public Health 2010; JAMA. 2010; 304:1584

Domande?

3a. Recent cancer screening recommendations from the USPSTF: Colorectal Cancer

2016 USPSTF Recommendation for CRC Screening

Draft: Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults ages 50 to 75 years	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years. The risks and benefits of different screening methods vary.	A
Adults ages 76 to 85 years	The decision to screen for colorectal cancer in adults ages 76 to 85 years should be an individual one, taking into account the patient's overall health and prior screening history. • Adults in this age group who have never been screened for colorectal cancer are more likely to benefit. • Screening would be most appropriate among adults who: 1) are healthy enough to undergo treatment if colorectal cancer is detected, and 2) do not have comorbid conditions that would significantly limit life expectancy.	C

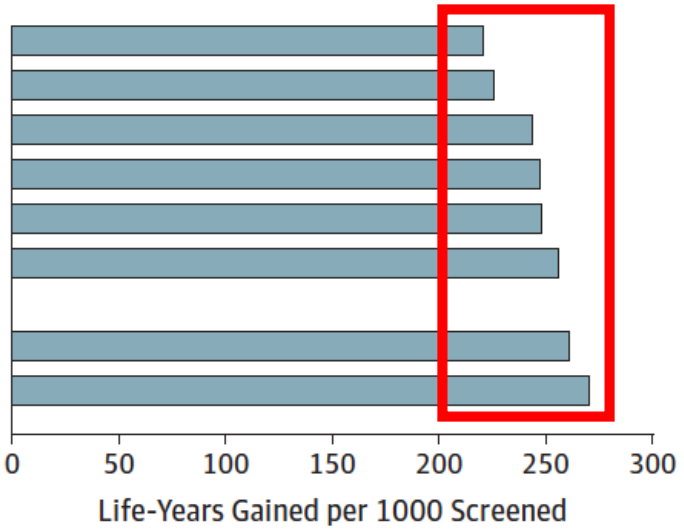
Italy: 50 to 69 years (or 74), fecal immunochemical test (FIT) every 2 years

Table. Characteristics of Colorectal Cancer Screening Strategies[a]

Screening Method	Frequency[b]	Evidence of Efficacy	Other Considerations
Stool-Based Tests			
gFOBT	Every year	RCTs with mortality end points: High-sensitivity versions (eg, Hemoccult SENSA) have superior test performance characteristics than older tests (eg, Hemoccult II)	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT[c]	Every year	Test characteristic studies: Improved accuracy compared with gFOBT Can be done with a single specimen	Does not require bowel preparation, anesthesia, or transportation to and from the screening examination (test is performed at home)
FIT-DNA	Every 1 or 3 y[d]	Test characteristic studies: Specificity is lower than for FIT, resulting in more false-positive results, more diagnostic colonoscopies, and more associated adverse events per screening test Improved sensitivity compared with FIT per single screening test	There is insufficient evidence about appropriate longitudinal follow-up of abnormal findings after a negative diagnostic colonoscopy; may potentially lead to overly intensive surveillance due to provider and patient concerns over the genetic component of the test
Direct Visualization Tests			
Colonoscopy[c]	Every 10 y	Prospective cohort study with mortality end point	Requires less frequent screening Screening and diagnostic follow-up of positive findings can be performed during the same examination
CT colonography[e]	Every 5 y	Test characteristic studies	There is insufficient evidence about the potential harms of associated extracolonic findings, which are common
Flexible sigmoidoscopy	Every 5 y	RCTs with mortality end points: Modeling suggests it provides less benefit than when combined with FIT or compared with other strategies	Test availability has declined in the United States
Flexible sigmoidoscopy with FIT[c]	Flexible sigmoidoscopy every 10 y plus FIT every year	RCT with mortality end point (subgroup analysis)	Test availability has declined in the United States Potentially attractive option for patients who want endoscopic screening but want to limit exposure to colonoscopy

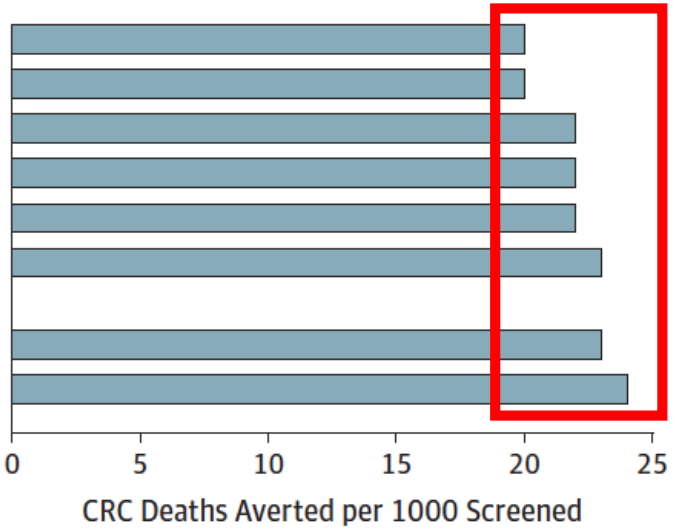
A Benefit: Life-years gained per 1000 individuals screened

Screening Method and Frequency	Model Estimates, Life-Years Gained per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	221	181	227
FIT-DNA every 3 y	226	215	250
FIT every year[a]	244	231	260
HSgFOBT every year	247	232	261
CT colonography every 5 y[b]	248	226	265
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	256	246	270
FIT-DNA every year	261	246	271
Colonoscopy every 10 y[a]	270	248	275



B Benefit: Colorectal cancer deaths averted per 1000 individuals screened

Screening Method and Frequency	Model Estimates, CRC Deaths Averted per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	20	17	21
FIT-DNA every 3 y	20	19	22
FIT every year[a]	22	20	23
HSgFOBT every year	22	20	23
CT colonography every 5 y[b]	22	20	24
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	23	22	24
FIT-DNA every year	23	22	24
Colonoscopy every 10 y[a]	24	22	24



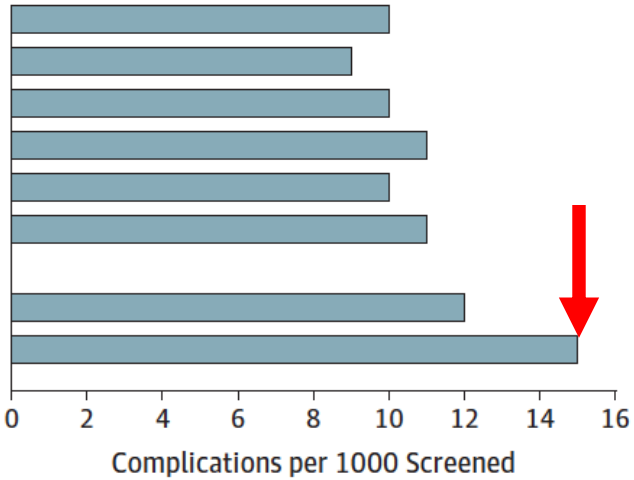
Potential benefits:

Per 1000 persons screened:

- 221 to 270 life years gained
- 20 to 24 fewer deaths due to colorectal cancer

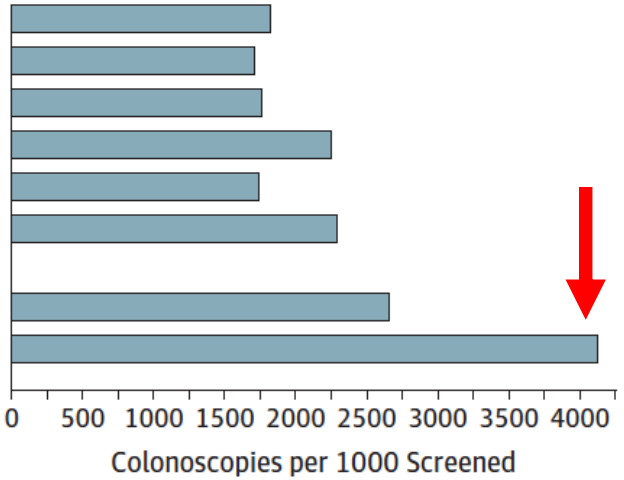
C Harms: Complications (gastrointestinal and cardiovascular events) of colorectal cancer screening and follow-up testing per 1000 individuals screened[c]

Screening Method and Frequency	Model Estimates, Complications per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	10	9	12
FIT-DNA every 3 y	9	9	10
FIT every year[a]	10	10	11
HSgFOBT every year	11	11	11
CT colonography every 5 y[b]	10	10	11
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	11	11	12
FIT-DNA every year	12	12	13
Colonoscopy every 10 y[a]	15	14	15



D Burden: Lifetime No. of colonoscopies per 1000 individuals screened

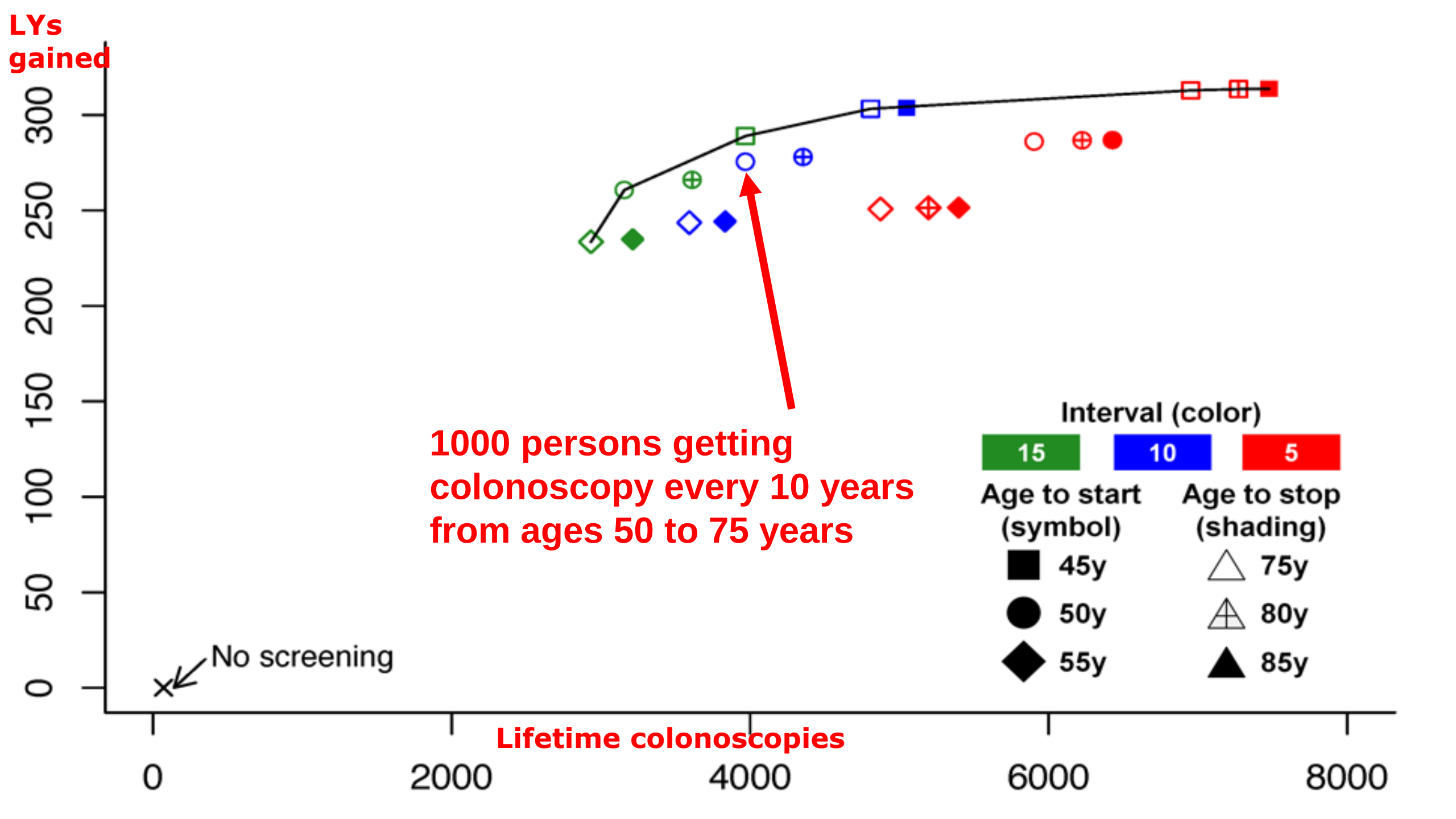
Screening Method and Frequency	Model Estimates, Lifetime Colonoscopies per 1000 Screened		
	Middle	Low	High
Flexible sigmoidoscopy every 5 y	1820	1493	2287
FIT-DNA every 3 y	1714	1701	1827
FIT every year[a]	1757	1739	1899
HSgFOBT every year	2253	2230	2287
CT colonography every 5 y[b]	1743	1654	1927
Flexible sigmoidoscopy every 10 y plus FIT every year[a]	2289	2248	2490
FIT-DNA every year	2662	2601	2729
Colonoscopy every 10 y[a]	4049	4007	4101

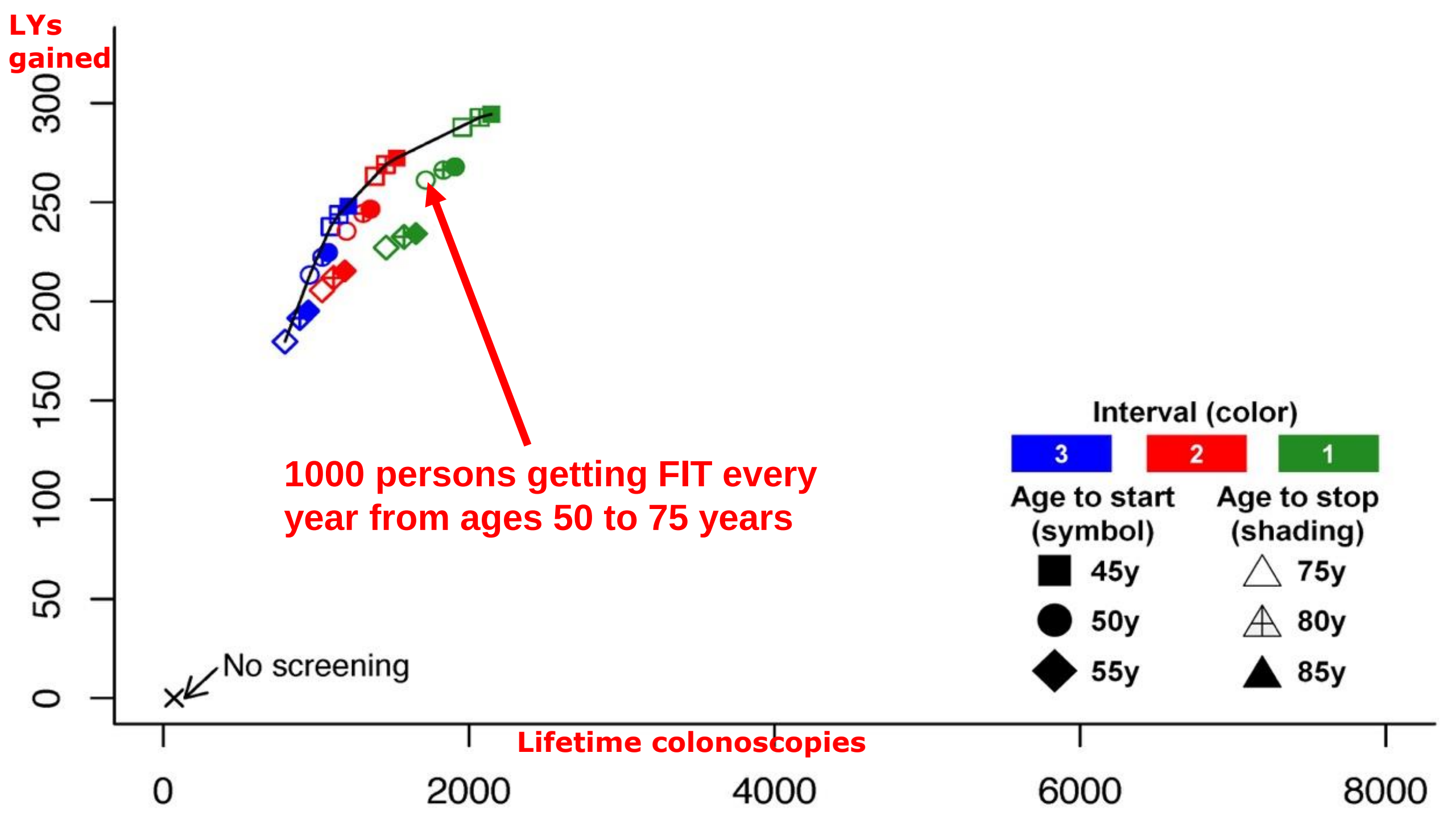


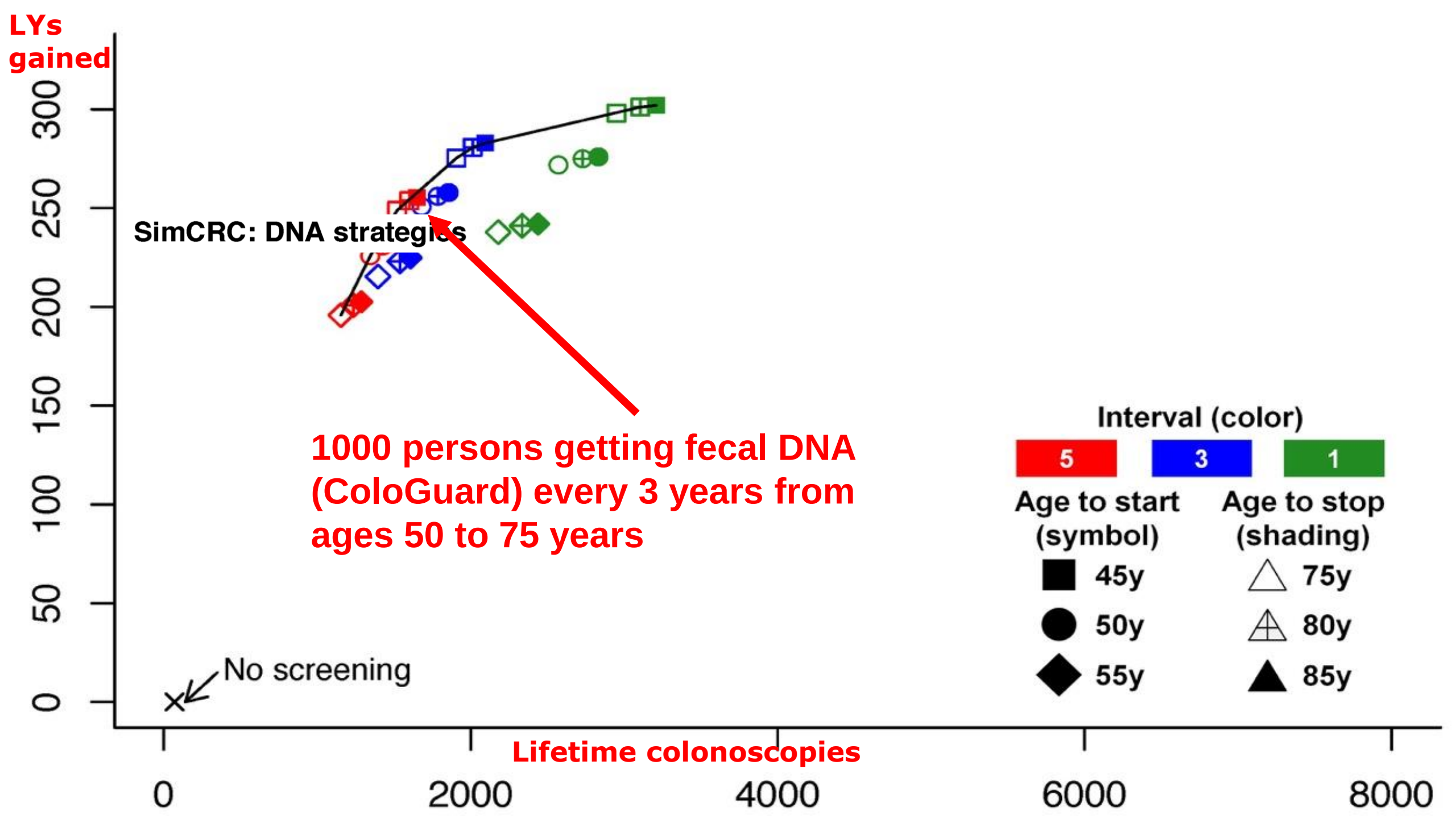
Potential harms and burden

Per 1000 persons screened:

- 9 to 15 complications
- 1.7 to 4.1 colonoscopies


LYs gained
300
250
200
150
100
50
0
1000 persons getting colonoscopy every 10 years from ages 50 to 75 years
Interval (color)
15
10
5
Age to start (symbol)
45y
50y
55y
Age to stop (shading)
75y
80y
85y
No screening
Lifetime colonoscopies
0
2000
4000
6000
8000


LYs gained
300
250
200
150
100
50
0
1000 persons getting FIT every year from ages 50 to 75 years
No screening
Interval (color)
3
2
1
Age to start (symbol)
Age to stop (shading)
45y
50y
55y
75y
80y
85y
Lifetime colonoscopies
0
2000
4000
6000
8000


LYs gained
300
250
200
150
100
50
0
SimCRC: DNA strategies
1000 persons getting fecal DNA (ColoGuard) every 3 years from ages 50 to 75 years
Interval (color)
5
3
1
Age to start (symbol)
Age to stop (shading)
45y
50y
55y
75y
80y
85y
No screening
Lifetime colonoscopies
0
2000
4000
6000
8000

Colorectal cancer screening strategies compared

Strategy (50 to 75 years)	Mean weeks gained/person	Lifetime colonoscopies/person	Lifetime cost of screening strategy
FIT test every 2 years	13.5 weeks	1.8	$1930
Colonoscopy every 10 years	14.5 weeks	4.0	$4000
Fecal DNA (Cologuard) every 3 years	13.0 weeks	1.8	$6600

Cost assumption: Colonoscopy = $1000, FIT = $10, Fecal DNA = $600
Benefit assumption: Benefit is evenly distributed across population
Harm assumption: The primary harms (burden, cost, complications) are directly associated with the number of lifetime colonoscopies

3b. Recent cancer screening recommendations from the USPSTF: Breast Cancer

Breast cancer screening: USPSTF 2016 Recommendation

- The USPSTF recommends biennial screening mammography for women aged 50 to 74 years. (B recommendation)
- The decision to start screening mammography in women prior to age 50 years should be an individual one. Women who place a higher value on the potential benefit than the potential harms may choose to begin biennial screening between 40 and 49 years. (C recommendation)
- Evidence is insufficient for women age 75 years and older (no clinical trial data) (I statement)

Additional comments re women 40 – 49 years

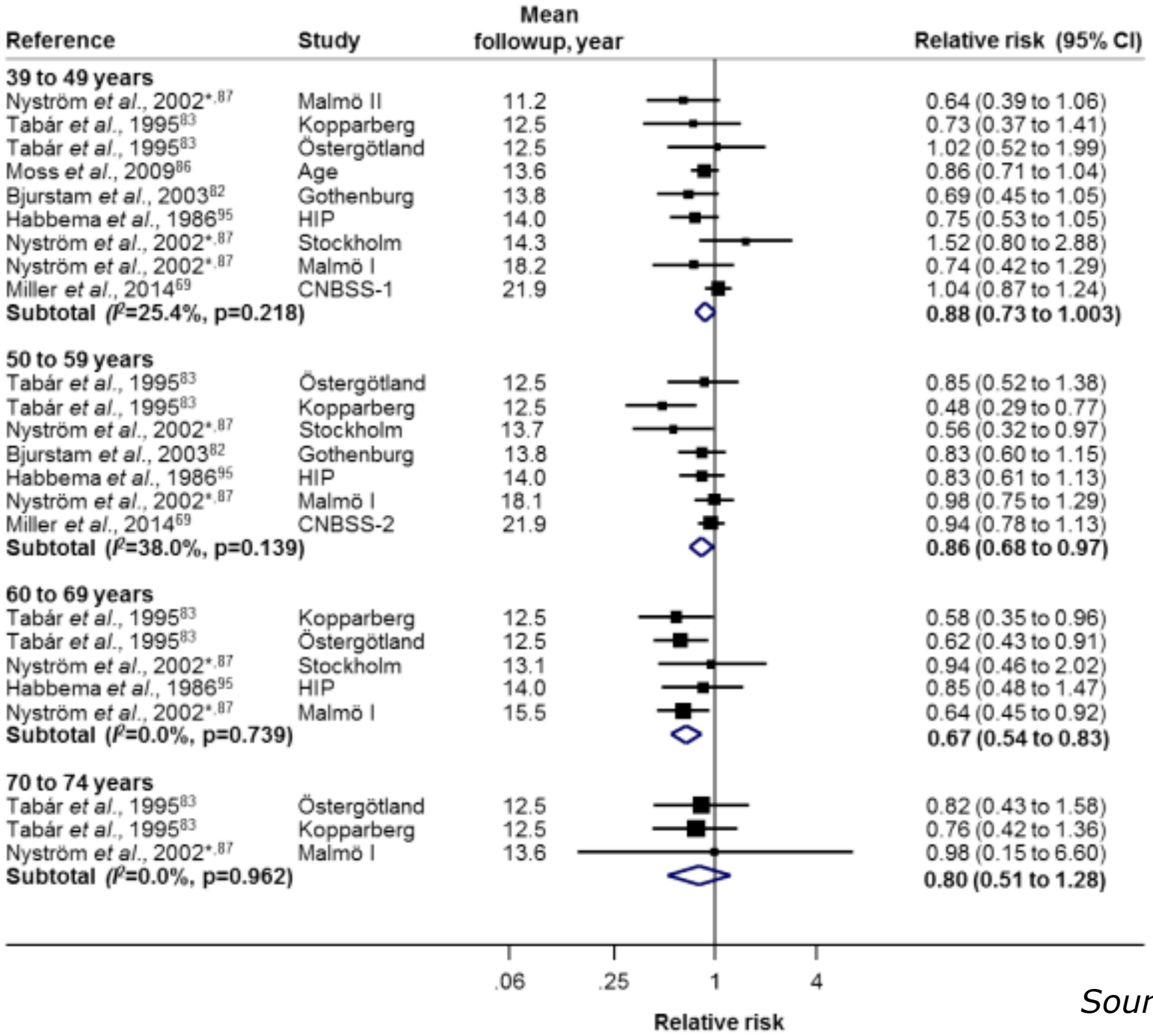
- For women at average risk for breast cancer, most of the benefit of mammography will result from biennial screening during ages 50 to 74 years. Of all age groups, women ages 60 to 69 years are most likely to avoid a breast cancer death through mammography screening.
- While screening mammography in women ages 40 to 49 years may reduce the risk of dying of breast cancer, the number of deaths averted is smaller than in older women and the number of false-positive tests and unnecessary biopsies are larger. The balance of benefits and harms improves as women move from their early 40's to their late 40's.
- All women undergoing regular screening mammography are at risk for the diagnosis and treatment of noninvasive and invasive breast cancer that would otherwise not have become a threat to her health, or even apparent, during her lifetime (known as "overdiagnosis"). Beginning mammography screening at a younger age and screening more frequently both increase this risk.
- Women with a parent, sibling, or child with breast cancer may benefit more than average-risk women from beginning screening between the ages of 40 and 49 years.

European Guidelines

Table 1 Breast cancer screening programme features by country or region in 26 European programmes (2007)

Country or region	Start (year)	Target age (years)	Interval (months)	Intermediate mammograms		Mammography views at screening (N)*
				After screening (Yes/No)	After further assessment (Yes/No)	
Belgium, Flanders	2001	50–69	24	Yes	No	2
Czech Republic	2002	45–69	24	Yes	Yes	2
Denmark, Copenhagen	1992	50–69	24	No	No	2/1
Estonia	2002	50–59	24	No	Yes	2
Finland	1989	50–69	24	NA	NA	NA
Germany, pilot projects	2001	50–70	24	No	Yes	2
Hungary	2002	45–65	24	Yes	Yes	2
Italy	1990	50–69	24	Yes	Yes	2/1
Luxembourg	1992	50–69	24	Yes	No	2
Norway	1996	50–69	24	No	No	2
Poland	2007	50–69	24	Yes	Yes	2
Portugal, centre	1990	45–69	24	No	Yes	2
Portugal, north	1999	45–69	24	No	Yes	2
Republic of Ireland (East)	2000	50–64	24	No	Yes	2
Spain, Asturias	1991	50–69	24	No	Yes	2/1
Spain, Baleares	1990	50–64	24	Yes	Yes	2
Spain, Galicia	1992	50–66	24	Yes	Yes	2
Spain, Navarra	1990	45–69	24	Yes	Yes	2
Spain, Pais Vasco	1990	50–64	24	Yes	Yes	2
Spain, Valencia	1992	45–69	24	Yes	Yes	2/1
Sweden, Södermanland	1990	40–74	24	NA	NA	2/1
Sweden, Stockholm	1989	40–69	24	NA	NA	2/1
Sweden, Västmanland	1986	40–69	24	NA	NA	2/1
Switzerland, Fribourg	2004	50–70	24	No	Yes	2/1
The Netherlands	1988	50–75	24	NA	NA	2/1
UK, England	1988	50–70	36	No	Yes	2

Italy: age 50 to 69 years, every 2 years



Benefit: Relative risk of breast cancer specific mortality

39 to 49: 0.88 (0.73 – 1.00)

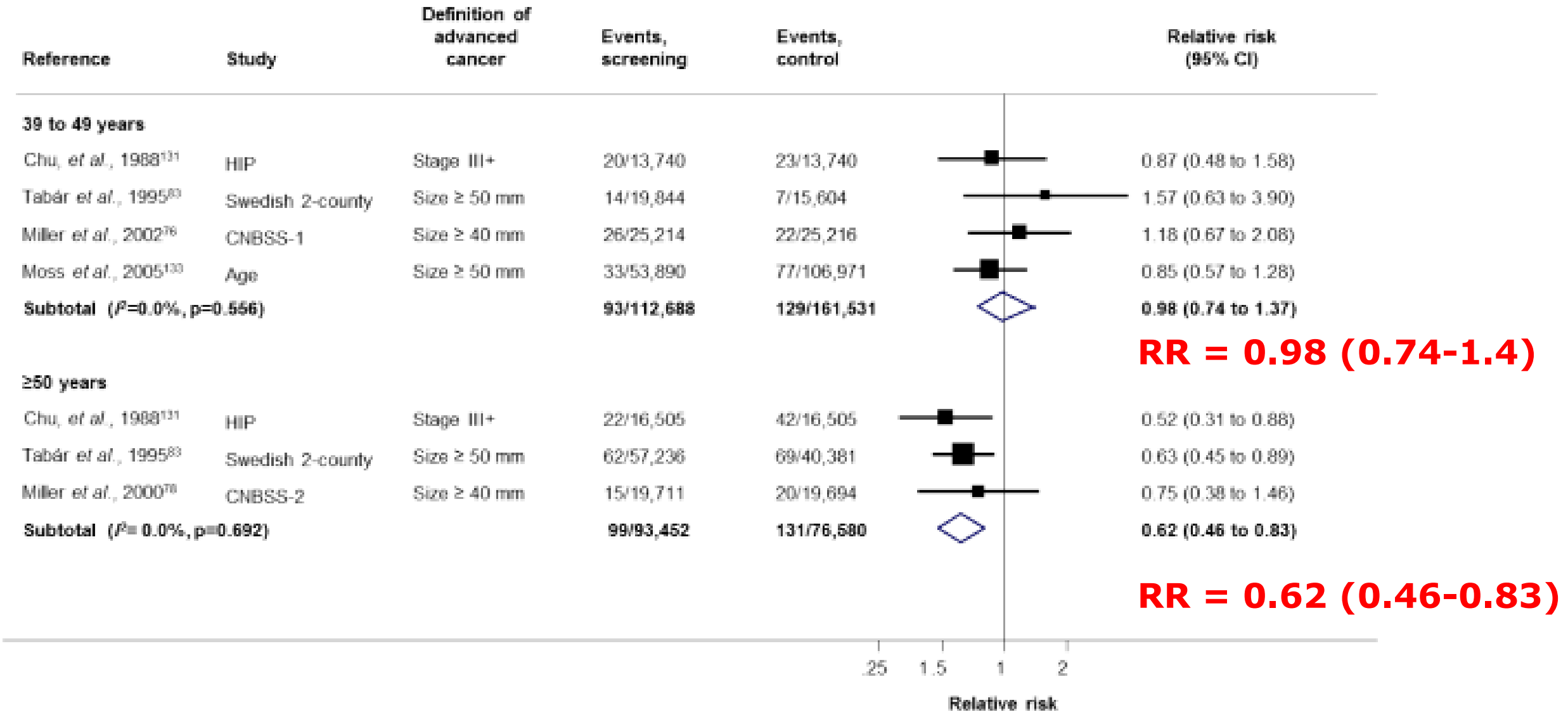
50 to 59: 0.86 (0.68 – 0.97)

60 to 69: 0.67 (0.54 – 0.83)

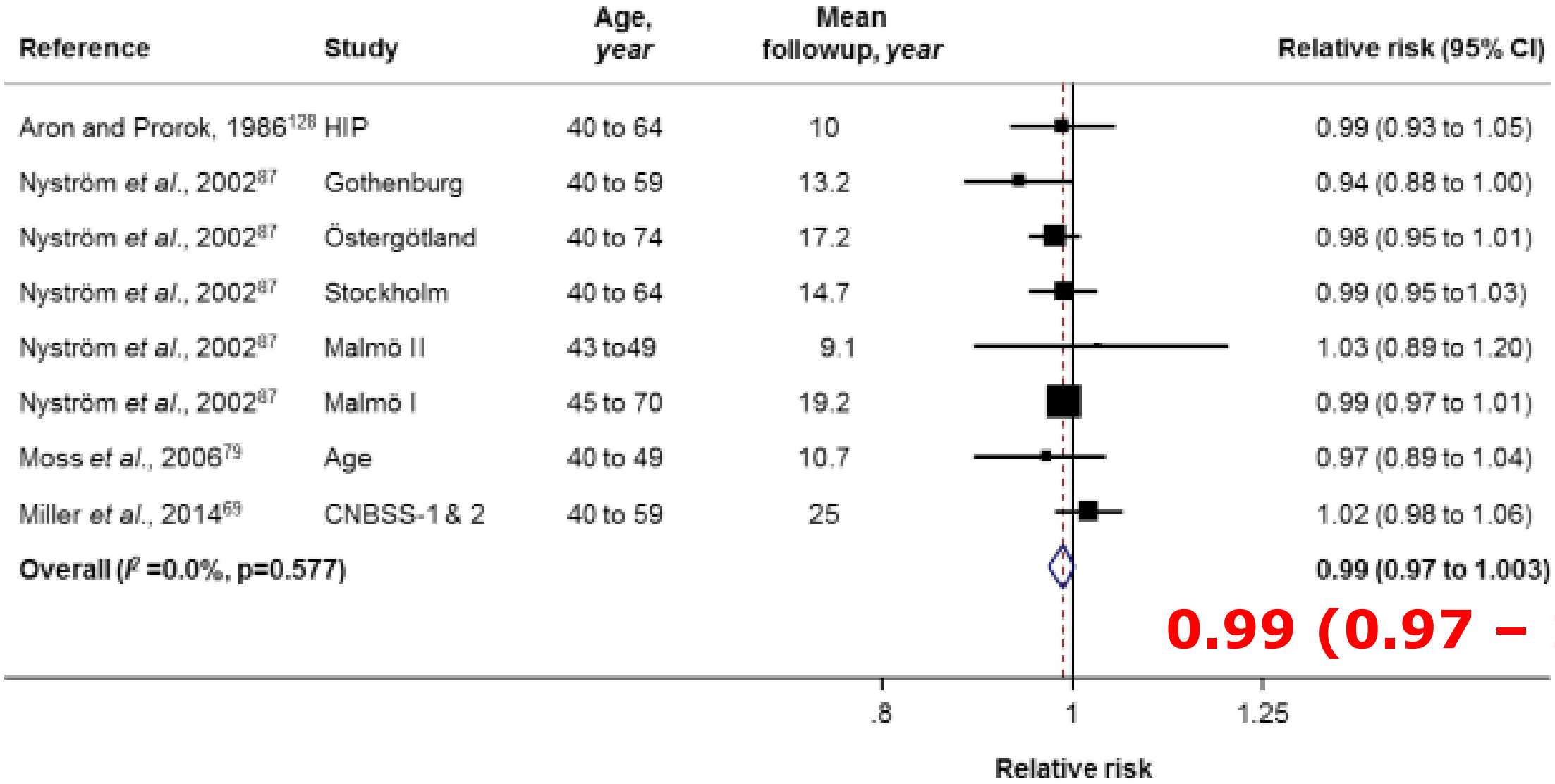
70 to 74: 0.80 (0.51 – 1.3)

Source: USPSTF evidence summary, 2016.

Benefit: Relative risk of Stage III/IV breast cancer

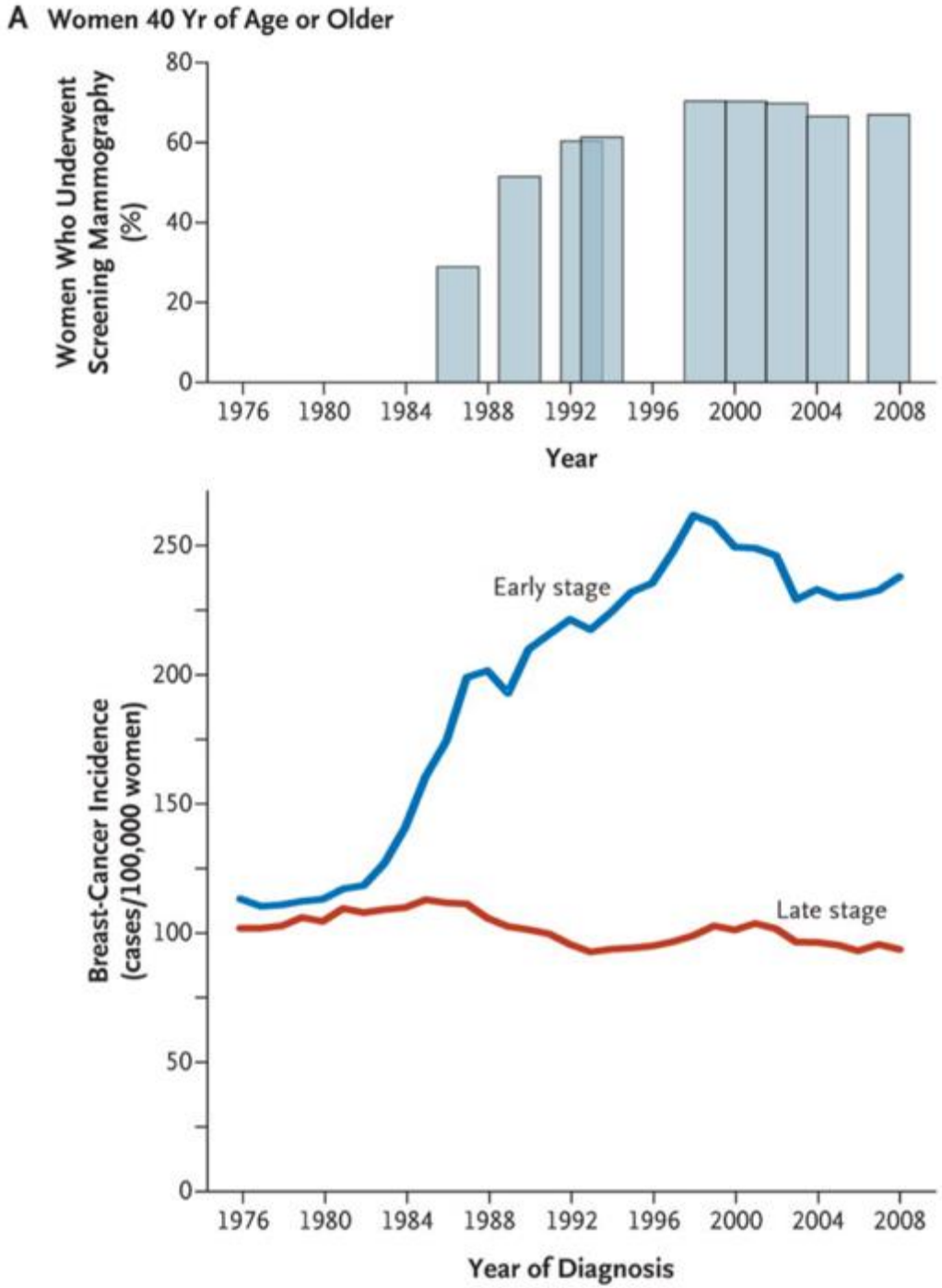


Benefit: Relative risk of all-cause mortality



0.99 (0.97 – 1.003)

Harms: Overdiagnosis and Treatment



Top graph: widespread mammography for women in 40's began in mid 1980's

Bottom graph: Large increase in incidence of early stage cancer: from 112 to 234 cases/100,000/year (blue line)

By now, we should have seen similar decline in late stage cancer. But, we have not: late stage only decreased from 102 to 94 cases/100,000/year (red line)

Best estimate: about 20% to 30% of breast cancers detected by screening are overdiagnosed

N Engl J Med 2013; 367: 1998

Lifetime benefits and harms for 1000 women screened starting at age 50 vs age 40 years

	Age 50 – 74 yrs Median (range)	Age 40 – 74 yrs Median (range)
Breast cancer deaths prevented -1	7 (4–9)	8 (5–10)
Life-years gained +30	122 (75–154)	152 (99–195)
False-positive tests +576	953 (830–1,325)	1,529 (1,100–1,976)
Unnecessary breast biopsies +58	146 (120–205)	204 (140–264)
Overdiagnosed breast tumors +2	19 (11–34)	21 (12–38)

3c. Recent cancer screening recommendations from the USPSTF: Prostate Cancer

2017 USPSTF Draft Recommendation

The U.S. Preventive Services Task Force's draft recommendations on screening for prostate cancer

For men 55–69, the decision to receive PSA-based screening should be between the clinician and the patient and include a complete understanding of all potential harms as well as benefits, and incorporate the patient's values and preferences. **(C grade)**

For men 70 and older, the U.S. Preventive Services Task Force recommends against PSA-based screening because the potential benefits do not outweigh the harms. **(D grade)**

This is a change – had been a "D" for "Do not screen for prostate cancer"

Guidelines from others

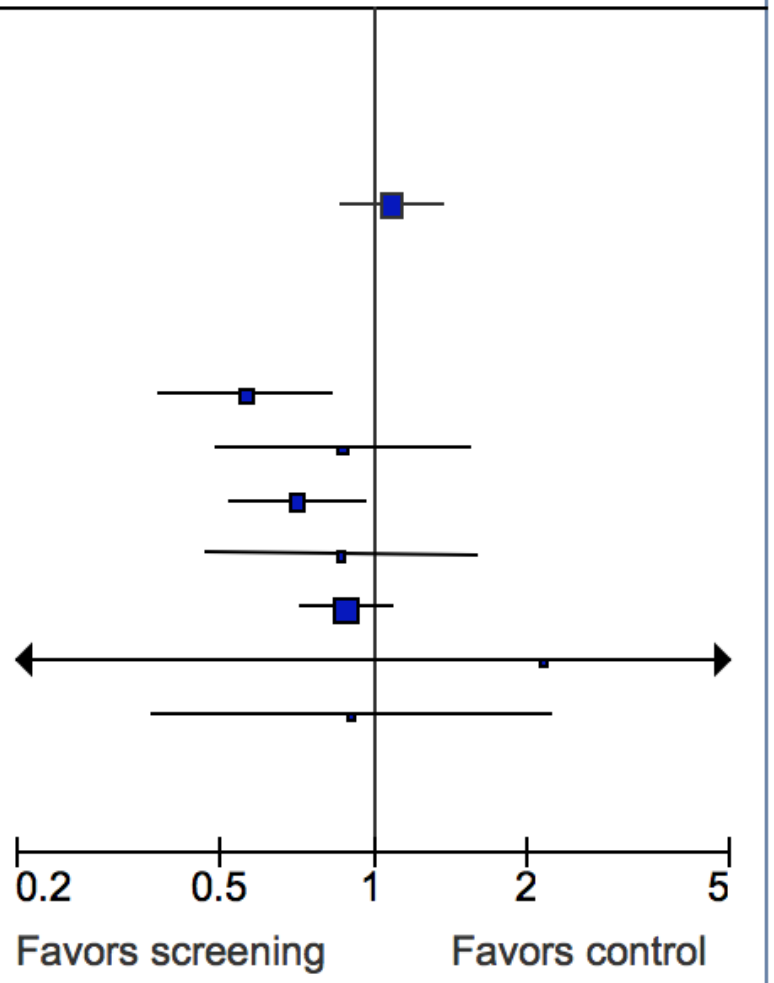
- American Urology Association (2013)
  - Discuss the option of screening with healthy men age 55 to 69 years
- American College of Physicians (2013)
  - Discuss benefits and harms with men age 55 to 69 years and offer PSA only to those who express a clear preference for screening

- List of countries NOT recommending PSA: Canada, UK, France, New Zealand
- **Italy: No organized screening program**

PLCO and ERSPC results

Figure 1. Relative risk of prostate cancer death for men screened with PSA versus controls, by country

Country	Screened Deaths	Screened Total	Control Deaths	Control Total	Risk Ratio [95% CI]
PLCO Trial					
United States	158	38340	145	38345	1.09 [0.87, 1.36]
ERSPC Trial					
Sweden	39	5901	70	5951	0.56 [0.38, 0.83]
Belgium	22	4307	25	4255	0.86 [0.48, 1.52]
Netherlands	69	17443	97	17390	0.71 [0.52, 0.96]
Italy	19	7266	22	7251	0.86 [0.46, 1.58]
Finland	139	31970	237	48409	0.89 [0.72, 1.09]
Spain	2	1056	1	1141	2.15 [0.20, 23.77]
Switzerland	9	4948	10	4955	0.89 [0.36, 2.20]



More screened in Italy, but fewer prostate cancers than Sweden. Why?

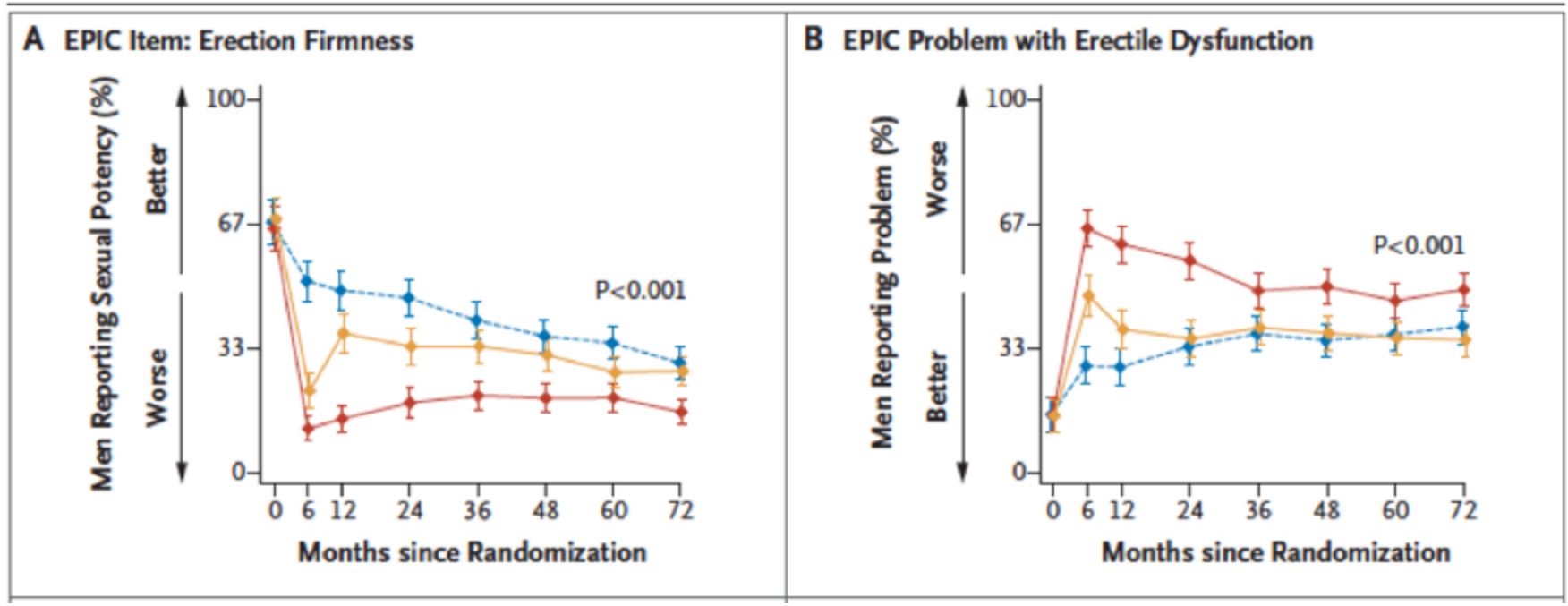
Harms of treatment

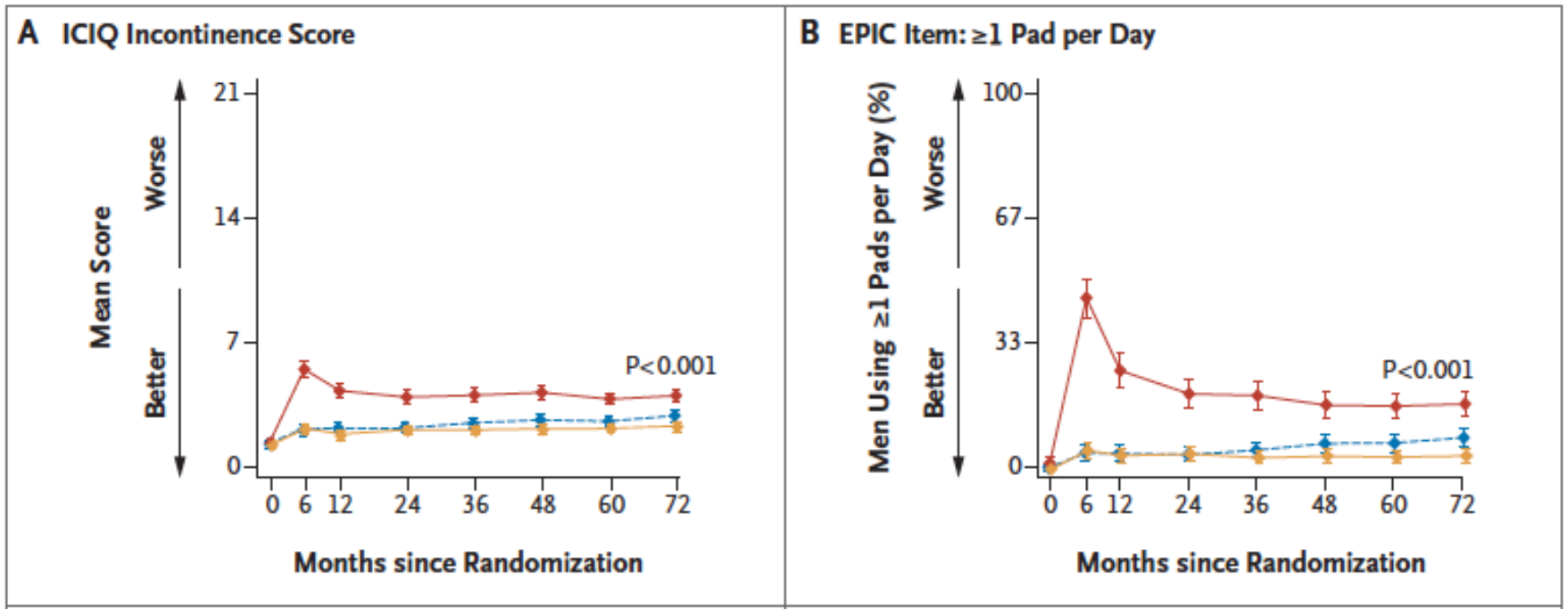
Erectile dysfunction

Radical prostatectomy
Radical radiotherapy
Active monitoring

Incontinence

Source: ProtecT Study. N Engl J Med 2016.





Arguments for and against using prostate cancer screening…

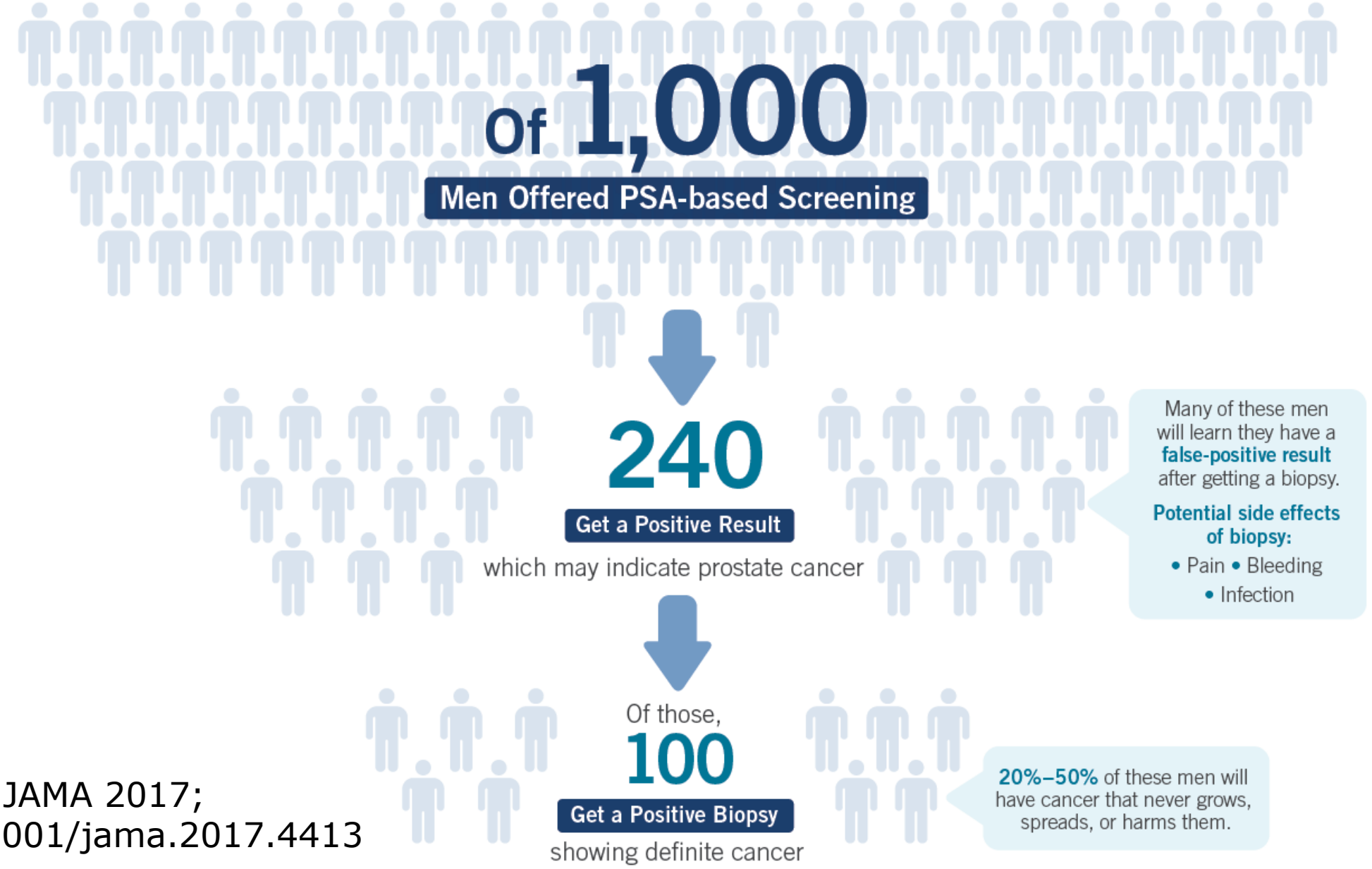
For:

- ERSPC found number needed to screen of 770 to prevent one prostate cancer death.
- Harms can be reduced by using active surveillance; only half with low risk cancer need treatment after 10 years.

Against:

- PLCO found no benefit; only Sweden and Netherlands in ERSPC had reduced cancer specific mortality. Other countries did not.
- Harms are substantial and overdiagnosis is common.
- No evidence for lower overall mortality

Prostate Screening Decision Aid



Source: JAMA 2017;
doi:10.1001/jama.2017.4413

Of those,

100

Get a Positive Biopsy

showing definite cancer

20%–50% of these men will have cancer that never grows, spreads, or harms them.

80*

Choose Surgery or Radiation Treatment

65

Choose immediate treatment

15

Choose treatment after a period of active surveillance

60 **or more** will experience serious complications

MEN

and/or

urinary incontinence

sexual impotence

3

Avoid Cancer Spreading

to other organs

1–2

Avoid Death From Prostate Cancer

Source: JAMA 2017;
doi:10.1001/jama.2017.4413

Domande?

4a. Recent USPSTF cardiovascular prevention recommendations: Aspirin

2015 USPSTF Recommendations

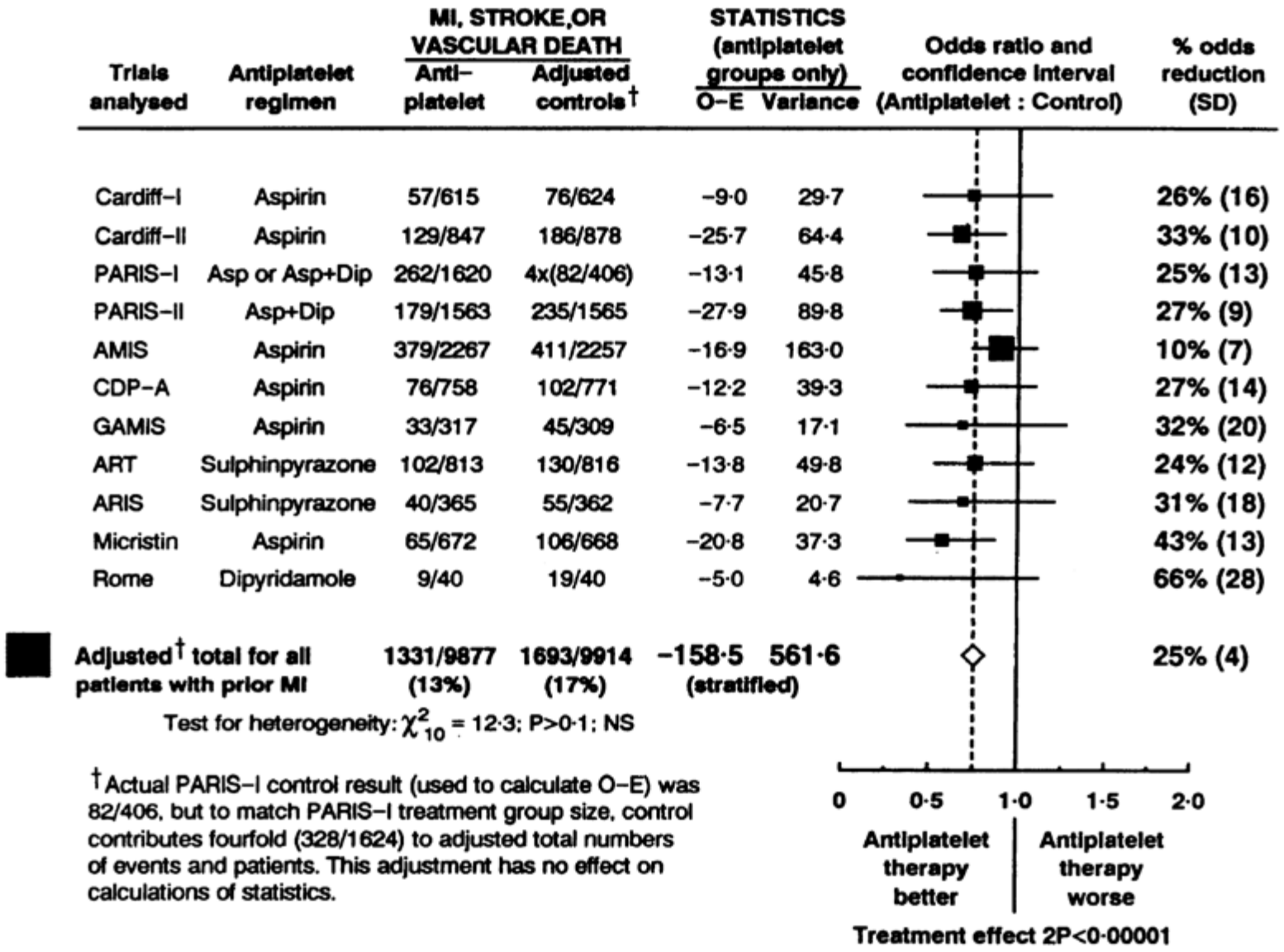
Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 50 to 59 years with a ≥10% 10-year CVD risk	The USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and colorectal cancer (CRC) in adults aged 50 to 59 years who have a 10% or greater 10-year CVD risk, are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years.	B
Adults aged 60 to 69 years with a ≥10% 10-year CVD risk	The decision to initiate low-dose aspirin use for the primary prevention of CVD and CRC in adults aged 60 to 69 years who have a 10% or greater 10-year CVD risk should be an individual one. Persons who are not at increased risk for bleeding, have a life expectancy of at least 10 years, and are willing to take low-dose aspirin daily for at least 10 years are more likely to benefit. Persons who place a higher value on the potential benefits than the potential harms may choose to initiate low-dose aspirin.	C
Adults younger than 50 years	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults younger than 50 years.	I
Adults aged 70 years or older	The current evidence is insufficient to assess the balance of benefits and harms of initiating aspirin use for the primary prevention of CVD and CRC in adults aged 70 years or older.	I

CV Benefit

- First meta-analysis in 1994
- Aspirin reduced composite of MI, stroke, or CV death:
  - 13% vs 17%
  - Absolute risk reduction = 4%
  - Number needed to treat = 25
  - Relative risk reduction ~ 25%

BMJ 1994; 308:81-106.



Trials analysed	Antiplatelet regimen	MI, STROKE, OR VASCULAR DEATH: Anti-platelet	MI, STROKE, OR VASCULAR DEATH: Adjusted controls†	STATISTICS (antiplatelet groups only): O–E	STATISTICS (antiplatelet groups only): Variance	% odds reduction (SD)
Cardiff–I	Aspirin	57/615	76/624	−9·0	29·7	26% (16)
Cardiff–II	Aspirin	129/847	186/878	−25·7	64·4	33% (10)
PARIS–I	Asp or Asp+Dip	262/1620	4x(82/406)	−13·1	45·8	25% (13)
PARIS–II	Asp+Dip	179/1563	235/1565	−27·9	89·8	27% (9)
AMIS	Aspirin	379/2267	411/2257	−16·9	163·0	10% (7)
CDP–A	Aspirin	76/758	102/771	−12·2	39·3	27% (14)
GAMIS	Aspirin	33/317	45/309	−6·5	17·1	32% (20)
ART	Sulphinpyrazone	102/813	130/816	−13·8	49·8	24% (12)
ARIS	Sulphinpyrazone	40/365	55/362	−7·7	20·7	31% (18)
Micristin	Aspirin	65/672	106/668	−20·8	37·3	43% (13)
Rome	Dipyridamole	9/40	19/40	−5·0	4·6	66% (28)
Adjusted† total for all patients with prior MI		**1331/9877 (13%)**	**1693/9914 (17%)**	**−158·5 (stratified)**	**561·6**	25% (4)

Test for heterogeneity: χ^2_{10} = 12·3; P>0·1; NS

†Actual PARIS–I control result (used to calculate O–E) was 82/406, but to match PARIS–I treatment group size, control contributes fourfold (328/1624) to adjusted total numbers of events and patients. This adjustment has no effect on calculations of statistics.

But...

But what about low risk patients?

CV events only slightly reduced:

4.4% vs 4.8% over 5 years

Absolute risk reduction = 0.4%

Number needed to treat over 5 years = 250

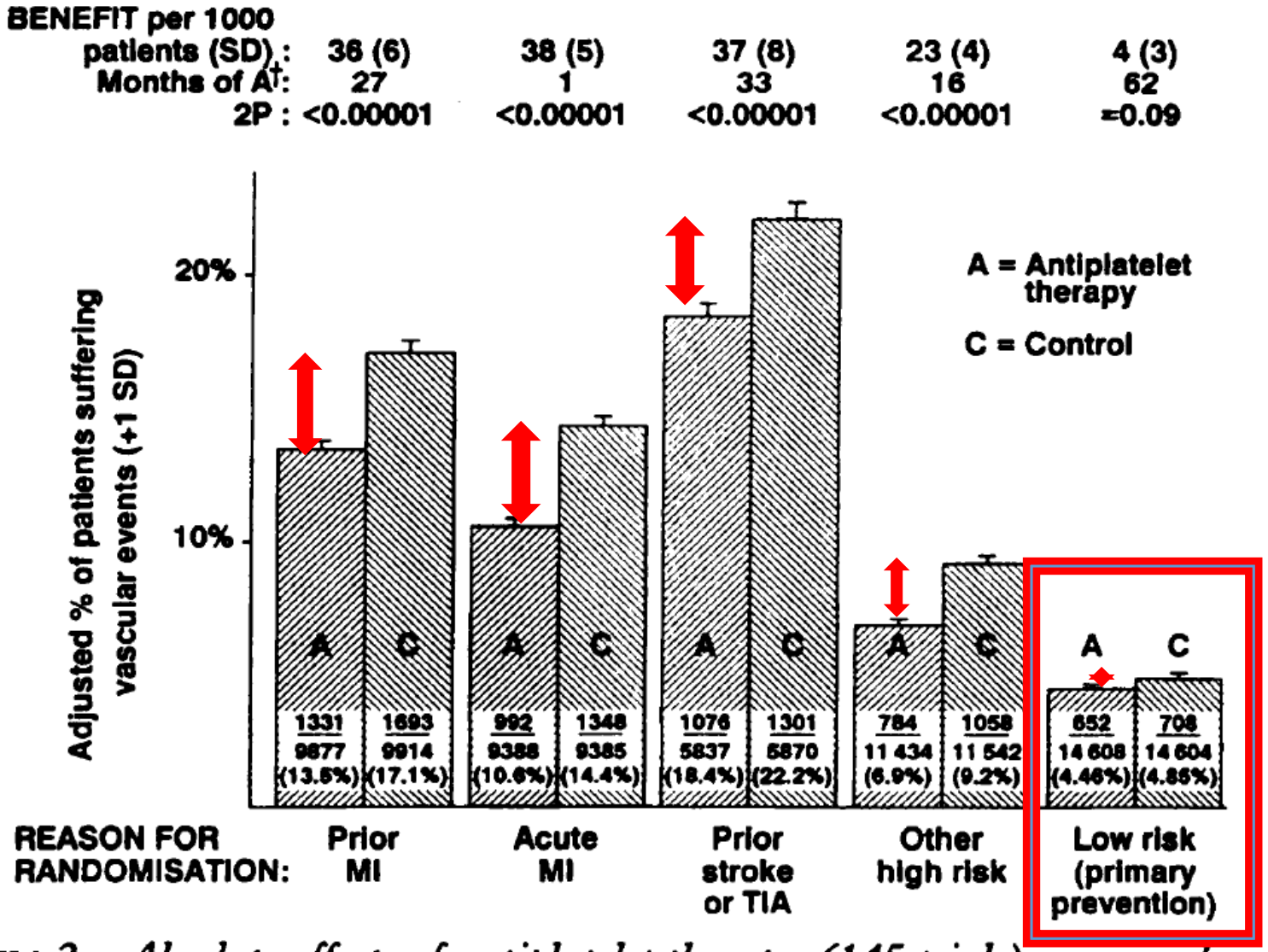


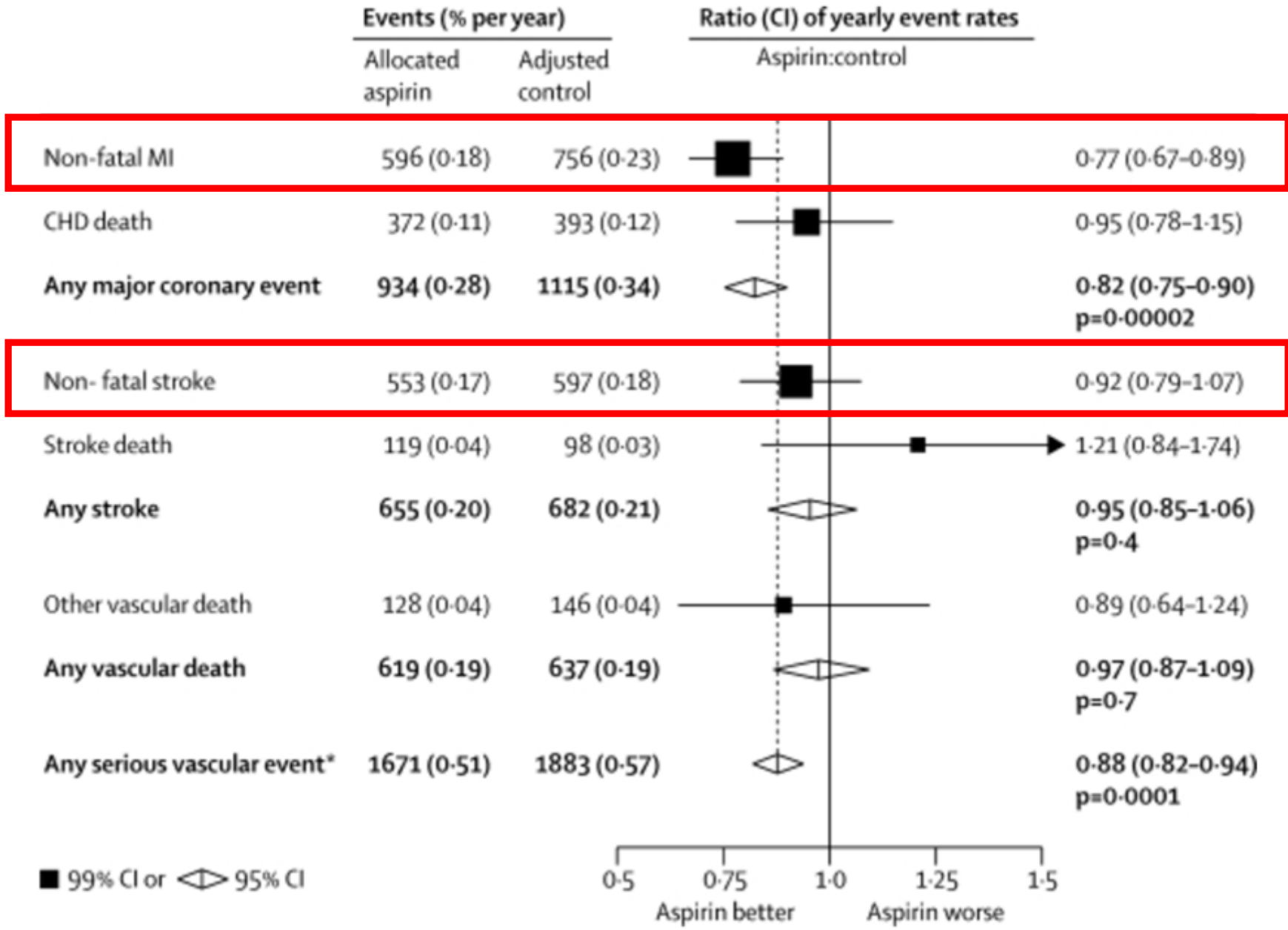
FIG 3—*Absolute effects of antiplatelet therapy (145 trials) on vascular events (myocardial infarction, stroke, or vascular death) in four main high risk categories of trial and in low risk (primary prevention)*

Individual patient data meta-analysis of CV outcomes
(*Rothwell, 2009, Lancet*)

Primary prevention trials only

What exactly is reduced?

Most of benefit is preventing non-fatal MI and non-fatal stroke



Serious vascular events in primary prevention trials—proportional effects of aspirin allocation

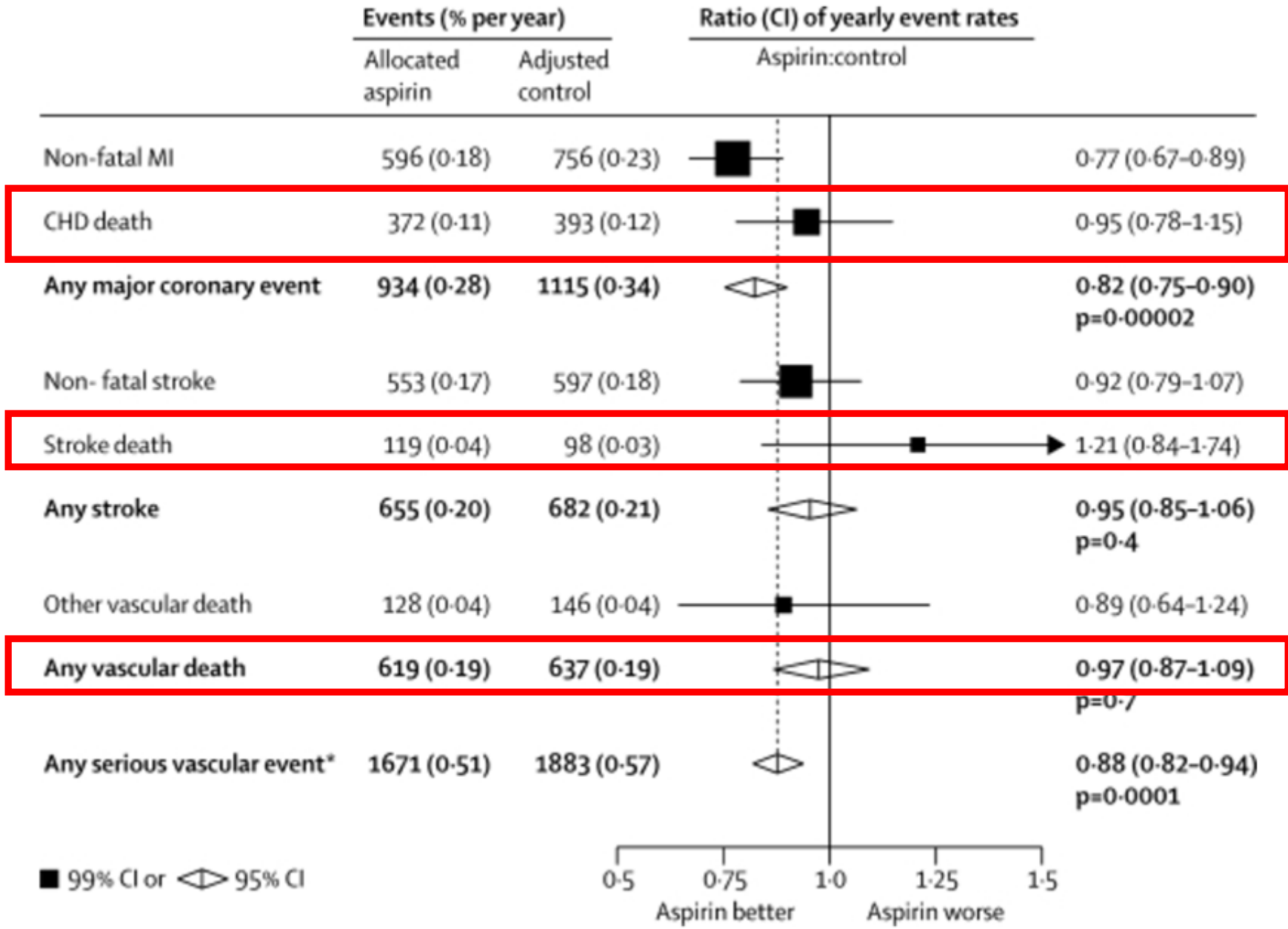
Individual patient data meta-analysis of CV outcomes

(*Rothwell, 2009, Lancet*)

Primary prevention trials only

What exactly is reduced?

No effect on CHD death, stroke death, or any vascular death



Serious vascular events in primary prevention trials—proportional effects of aspirin allocation

Prevention of solid tumors (especially colorectal cancer)

Risk of cancer death by duration of aspirin therapy

red = aspirin

blue = placebo

Key point: need to take aspirin for at least 7 to 10 years to see the benefit

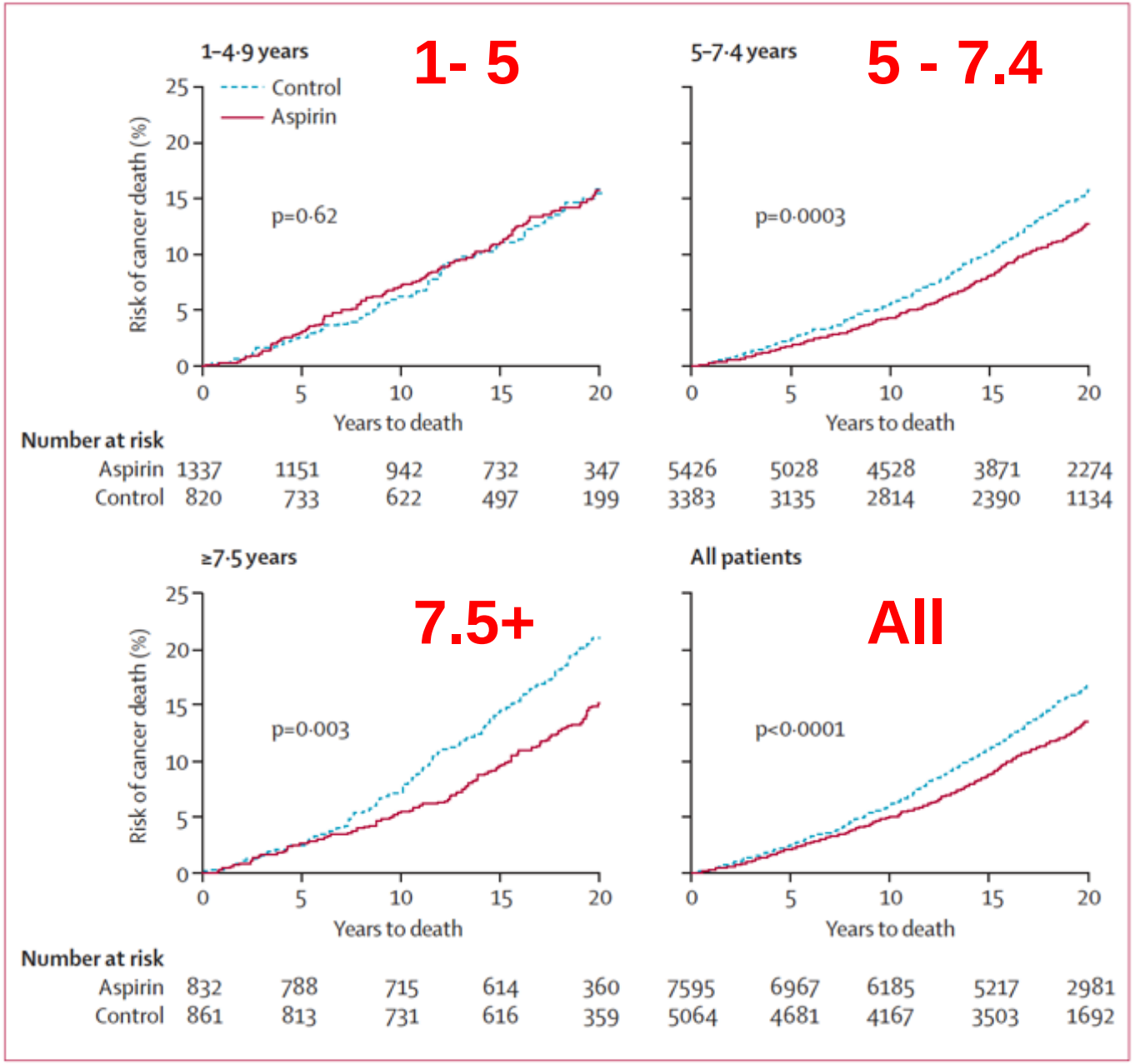


Figure 3: **Effect of allocation to aspirin versus control on 20-year risk of death due to any solid cancer stratified by scheduled duration of trial treatment in three trials with long-term follow-up[17-19]**

Continuous variable interaction, p=0·01.

What about harms?

Excess bleeding risk (greater with higher baseline risk)

About 1 more major GI bleed per 3600 person-years
About 1 more intracranial hemorrhage per 7000 person-years
About 1 more hemorrhagic stroke per 10,000 person-years

Table 3. Absolute Events Caused or Prevented With Very-Low-Dose Aspirin Use for ≤10 y*

Outcome	Risk Level†	Baseline Risk for Outcome, *events per 1000 person-years*	Relative Risk (95% CI)	Events Caused per 1000 Person-Years (95% CI)‡
Major GIB§ (k = 5)	Low	0.23	1.58 (1.29 to 1.95)	0.13 (0.07 to 0.22)
	Median	0.49		0.28 (0.14 to 0.46)
	High	0.58		0.34 (0.17 to 0.55)
	Highest	1.04		0.60 (0.30 to 0.99)
ICH, including HS (k = 8)	Low	0.20	1.30 (1.00 to 1.68)	0.06 (0.00 to 0.14)
	Median	0.47		0.14 (0.00 to 0.32)
	High	0.59		0.18 (0.00 to 0.40)
	Highest	1.25		0.38 (0.00 to 0.85)
HS (k = 7)	Low	0.00	1.27 (0.96 to 1.68)	0.00 (0.00 to 0.00)
	Median	0.37		0.10 (−0.01 to 0.25)
	High	0.42		0.11 (−0.02 to 0.29)
	Highest	1.26		0.34 (−0.05 to 0.86)
Major bleeding event	Cohort‖	2.4 (GIB)	1.58 (1.29 to 1.95) (GIB)¶	1.39 (0.70 to 2.28) (GIB)
		1.2 (HS)	1.27 (0.96 to 1.68) (HS)¶	0.32 (−0.05 to 0.82) (HS)
		3.6 (total)		1.71 (0.65 to 3.10) (total)
		3.6	1.55 (1.48 to 1.63)	1.98 (1.73 to 2.27)

Harms: So what does that really mean?

- Assuming that effect is linear, i.e. bleeding risk in year 1 is same as risk in year 20.
- Assuming a person starts on their 50th birthday and continues until age 69 years.
- You would get:
  - 1 more major GI bleed for every 180 people who take aspirin
  - 1 more major intracranial hemorrhage for every 350 people
  - 1 more major hemorrhage stroke for every 500 people

Overall: 1 of these events for every ~100 people taking aspirin for 20 years

Balancing Benefits a

Lifetime Events per 1,000 persons in

So…what do 64.4 QALYs gained per 1000 persons look like? If evenly distributed across population, that is 24 more days

CVD Risk	MIs Prevented	Ischemic Strokes Prevented	CRC Cases Prevented	Serious GI Bleeding Caused	Hemorrhagic Strokes Caused	Net Life-Years Gained	Quality-Adjusted Life-Years Gained
Ages 50 to 59 years							
10%	22.5	8.4	13.9	28.4	2.3	33.3	5[illegible].8
15%	26.7	8.6	12.1	26.0	2.8	39.5	64.4
20%	28.6	9.2	12.2	24.8	2.1	60.5	83.4
Ages 60 to 69 years							
10%	15.9	6.6	11.2	31.4	3.1	-2.0	18.0
15%	18.6	8.0	10.4	29.8	2.4	9.6	30.9
20%	20.1	8.4	9.1	26.7	2.7	11.6	31.8

Aspirin Bottom-Line

- Aspirin reduces non-fatal CV events, but more so in those at higher risk
- Aspirin reduces cancer deaths, but must be taken for 10 years to see that benefit
- Major bleeding events will occur in about 1 in 100 treated for 20 years

The net benefit (benefit – harm) is best for those at higher CV risk, low bleeding risk, and willing to take aspirin for 10+ years

4b. Recent USPSTF cardiovascular prevention recommendations: Statins

Recommendation Summary

Population	Recommendation	Grade (What's This?)
Adults aged 40 to 75 years with no history of CVD, 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 10% or greater	The USPSTF recommends that adults without a history of cardiovascular disease (CVD) (ie, symptomatic coronary artery disease or ischemic stroke) use a low- to moderate-dose statin for the prevention of CVD events and mortality when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 10% or greater. Identification of dyslipidemia and calculation of 10-year CVD event risk requires universal lipids screening in adults aged 40 to 75 years. See the "Clinical Considerations" section for more information on lipids screening and the assessment of cardiovascular risk.	B
Adults aged 40 to 75 years with no history of CVD, 1 or more CVD risk factors, and a calculated 10-year CVD event risk of 7.5% to 10%	Although statin use may be beneficial for the primary prevention of CVD events in some adults with a 10-year CVD event risk of less than 10%, the likelihood of benefit is smaller, because of a lower probability of disease and uncertainty in individual risk prediction. Clinicians may choose to offer a low- to moderate-dose statin to certain adults without a history of CVD when all of the following criteria are met: 1) they are aged 40 to 75 years; 2) they have 1 or more CVD risk factors (ie, dyslipidemia, diabetes, hypertension, or smoking); and 3) they have a calculated 10-year risk of a cardiovascular event of 7.5% to 10%.	C

Recommended if 40 to 75 years old with 1 or more CV risk factors and:

-- 10 year CV event risk of 10% or higher (B recommendation)

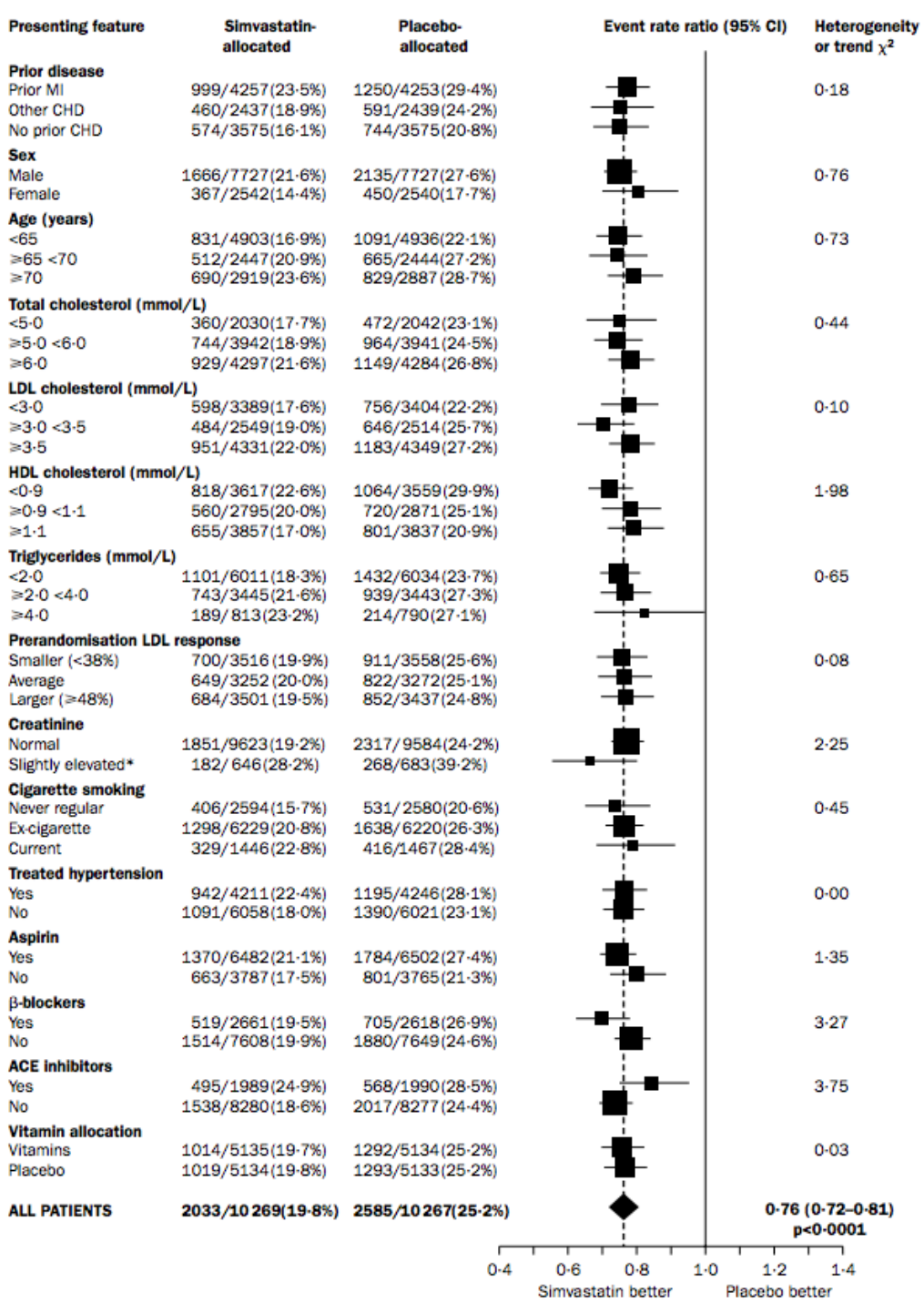
-- 10 year 7.5% - 10% (C recommendation)

2013 ACC/AHA Guidelines

“Therefore, given the absence of data on titration of drug therapy to specific goals, no recommendations are made for or against specific LDL–C or non-HDL–C goals for the primary or secondary prevention of ASCVD.”

Treatment recommendations are now based on statin dose, not LDL target.

- Anyone <= 75 years with known vascular disease or LDL > 190 mg/dL should receive a **high-intensity statin**.
- Anyone > 75 years with known vascular disease and anyone with diabetes should receive a **moderate-intensity statin**.
- If someone with diabetes has a 10-year risk of at least 7.5%, they should instead be given a **high-intensity statin**.
- If any patient without diabetes has a 10-year risk of at least 7.5%, they should receive a **moderate or high-intensity statin**.
- 10 year risk of 5% to 7.5%, **discuss with patient**

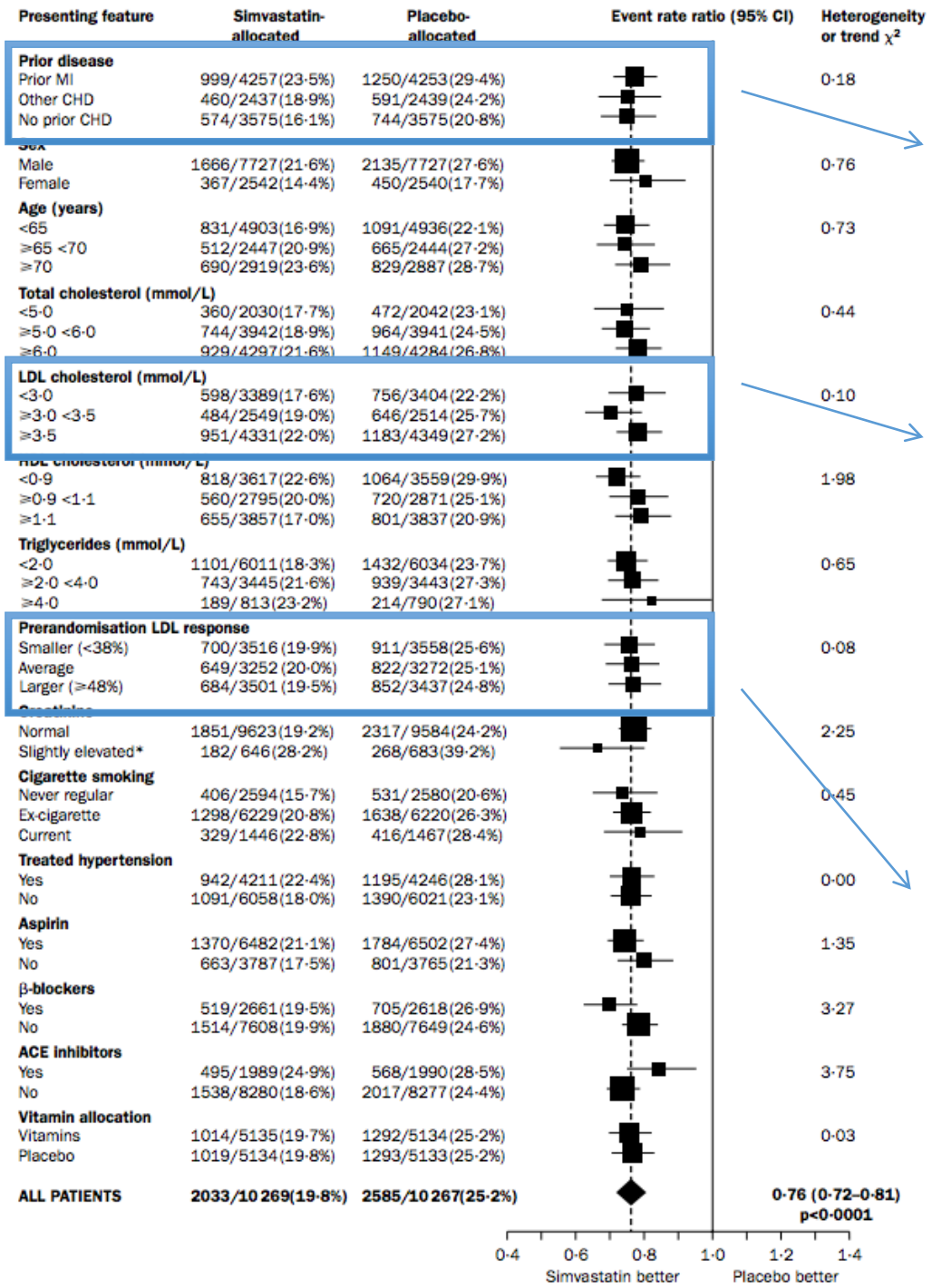


Important shift in US guidelines: Treat to target or not?

Heart Protection Study

Interesting finding: relative risk reduction was similar for all subgroups

- Baseline cholesterol (even if quite low, LDL < 100 mg/dl)
- Prerandomization LDL response
- Smoking
- Hypertension
- Age
- Sex
- Primary vs tertiary prevention



Tertiary prevention: 29% RRR
Primary prevention: 21% RRR

Relative risk reduction by initial LDL cholesterol:

- < 100 mg/dl: 22%
- < 116 mg/dl: 21%
- 116 to 130 mg/dl: 26%
- > 130 mg/dl: 19%

Relative risk reduction by response to statin in terms of LDL reduction:

- Smaller: 22%
- Average: 20%
- Larger: 21%

So, benefit was not tied to how much the LDL was reduced

Let’s determine our risk

- http://clincalc.com/Cardiology/ASCVD/PooledCohort.aspx

- Guidelines differ regarding what is “high risk”:
  - ACC/AHA: 5% to 7.5%
  - USPSTF: 7.5% to 10%
  - US Veteran’s Affairs guideline: 12%

Decision Aids: Mayo Clinic

https://statindecisionaid.mayoclinic.org/

Lessons Learned

- Screening has potential benefits and harms; sometimes the harms (and costs) are greater than the benefits
- National guidelines based on the best available evidence can help reduce inappropriate practice variation
- Screening for colorectal cancer using FIT ever 1 to 2 years is preferable to colonoscopy every 10 years or fecal DNA
- Screening for breast cancer from 50 to 70 (or 75) years every 2 years provides the best balance of benefits and harms
- Prostate cancer screening is not a very good idea for most men
- Aspirin and statin benefit depends on risk assessment. But what is “high risk”?

Domande?