Evidence Based Medicine- How do you use it?

Conversations in risk reduction:
From evidence to decision making

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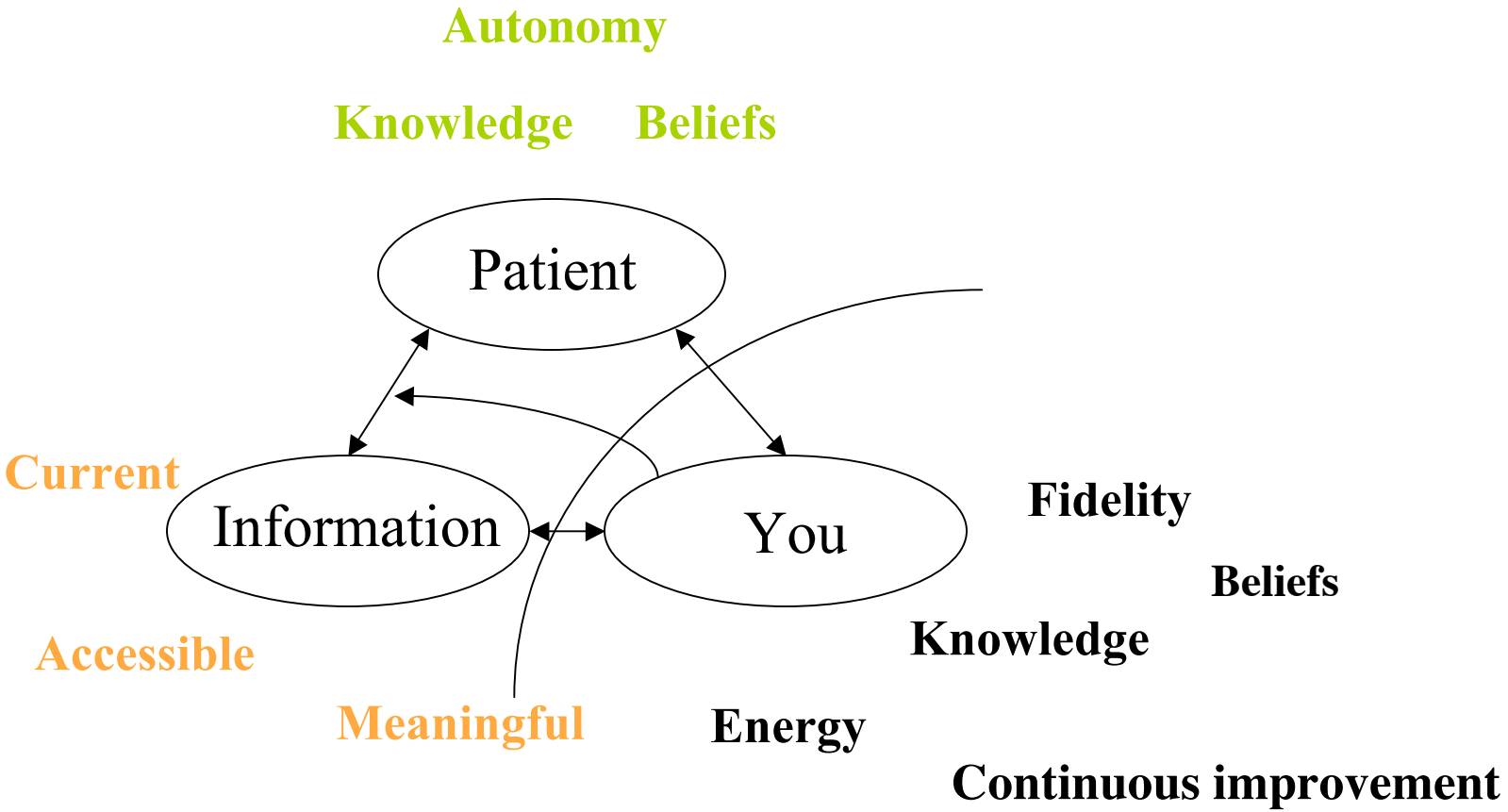
November 5, 2004

Learning objectives

- Review basics of EBM
- Discuss methods of communication of risk and risk reduction
- Explore the challenges of applying results of high quality clinical studies to patient care

The Encounter Paradigm



Hypothetic Examples of RRR, ARR & NNT Measures in 4 Studies

Group	Pts	# Events	RR	ARR	NNT
Placebo	**1000**	**1**	**50%**	**0.05%**	**2000**
Treated	**1000**	**0.5**			
Placebo	**1000**	**10**	**50%**	**0.5%**	**200**
Treated	**1000**	**5**			
Placebo	**1000**	**100**	**50%**	**5%**	**20**
Treated	**1000**	**50**			
Placebo	**1000**	**1000**	**50%**	**50%**	**2**
Treated	**1000**	**500**			

Number needed to….

- NNS- number needed to screen to prevent a particular outcome
  - (e.g. mammography/breast Ca)
- NNT- number needed to treat to prevent a particular outcome
  - (e.g. statins/CHD)
- NNH- number needed to harm to result in a particular outcome
  - (e.g. ASA and bleeding)

What is significant?

- Statistical significance
  - Epidemiologists, policy makers, population care advocates
- Clinical significance
  - Clinicians
- Personal significance
  - Patients

What is significant?

- RRR?
- ARR?
- P value < 0.05?
- Narrow Confidence Interval?

Desirable metrics:

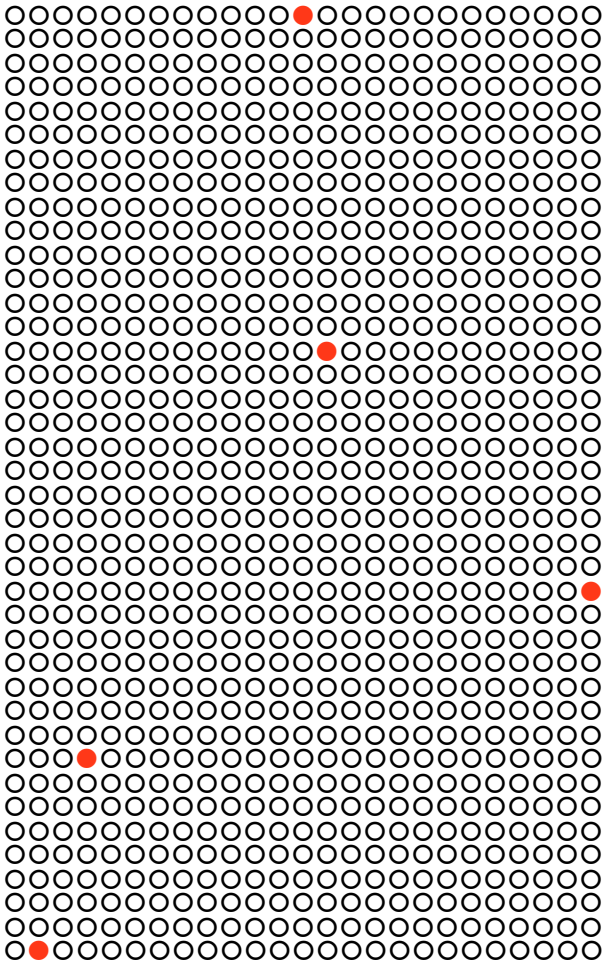
- NNS < 1000 for a screening test?
- NNT < 100 for a treatment effect?
- NNH > 200 for a harmful effect?

P values or confidence intervals?

- P values test the evidence against a null hypothesis- e.g. p=0.05 or we can be sure that the hypothesis tested is *likely to be true 95% of the time*.
- Confidence intervals tell us about the *strength of evidence*- e.g. a 95% CI is the range of values *within which we can be 95% sure that the true value lies*.

Risk reduction- relative (50%) or absolute (0.5%)?

5/1000
0.05%



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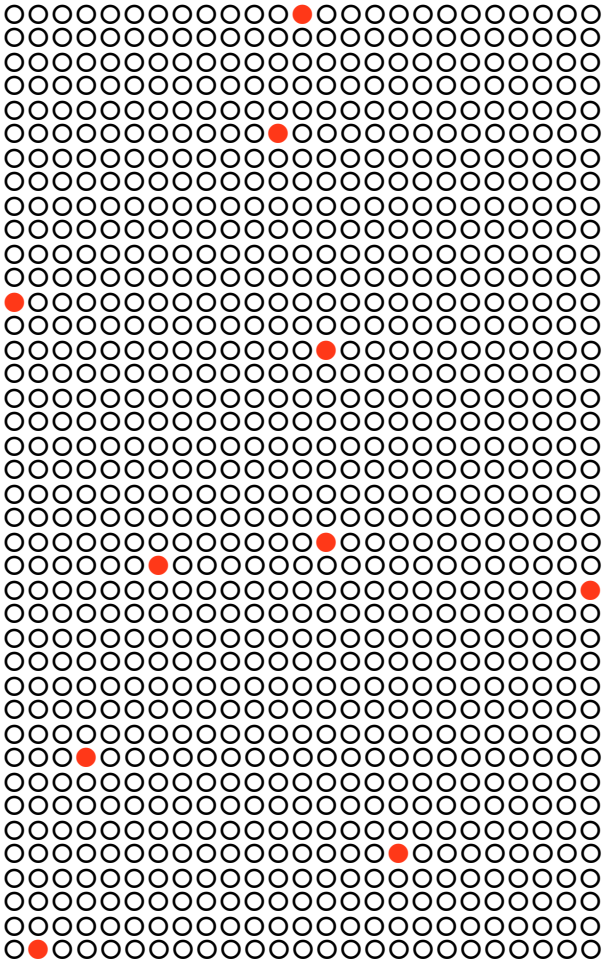
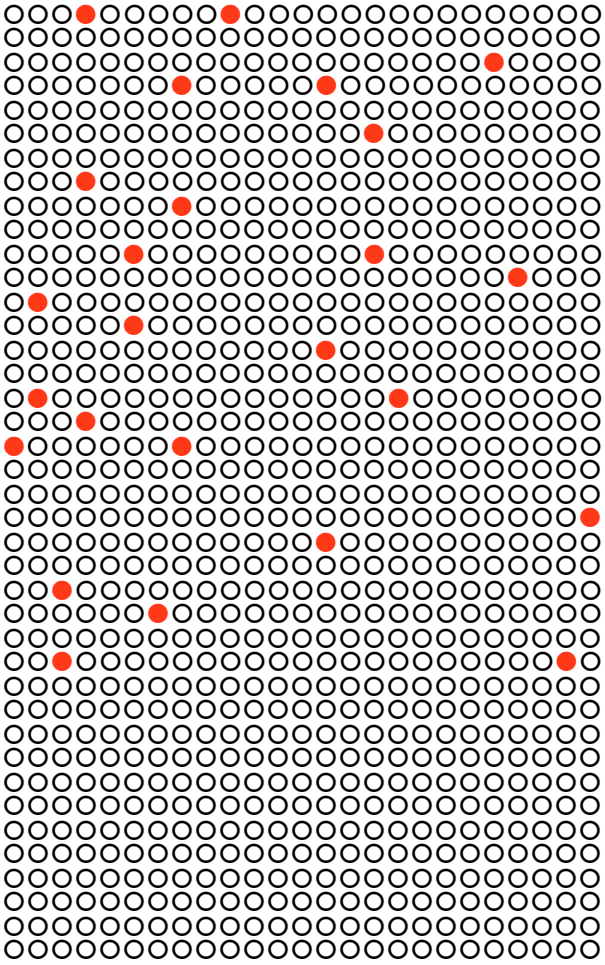


10/1000
0.10%

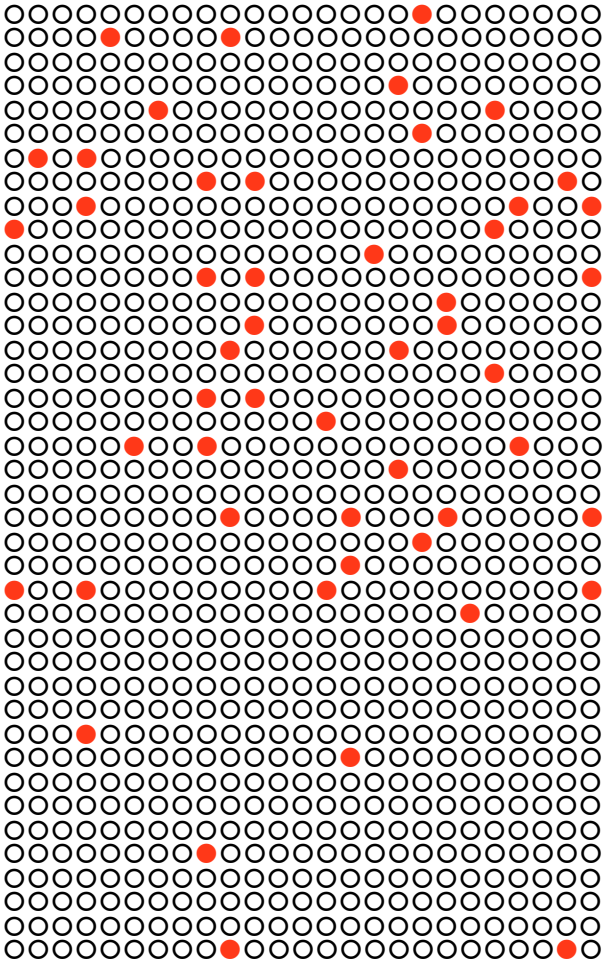
NNT 200

Risk reduction- relative (50%) or absolute (2.5%)?

25/1000
2.5%



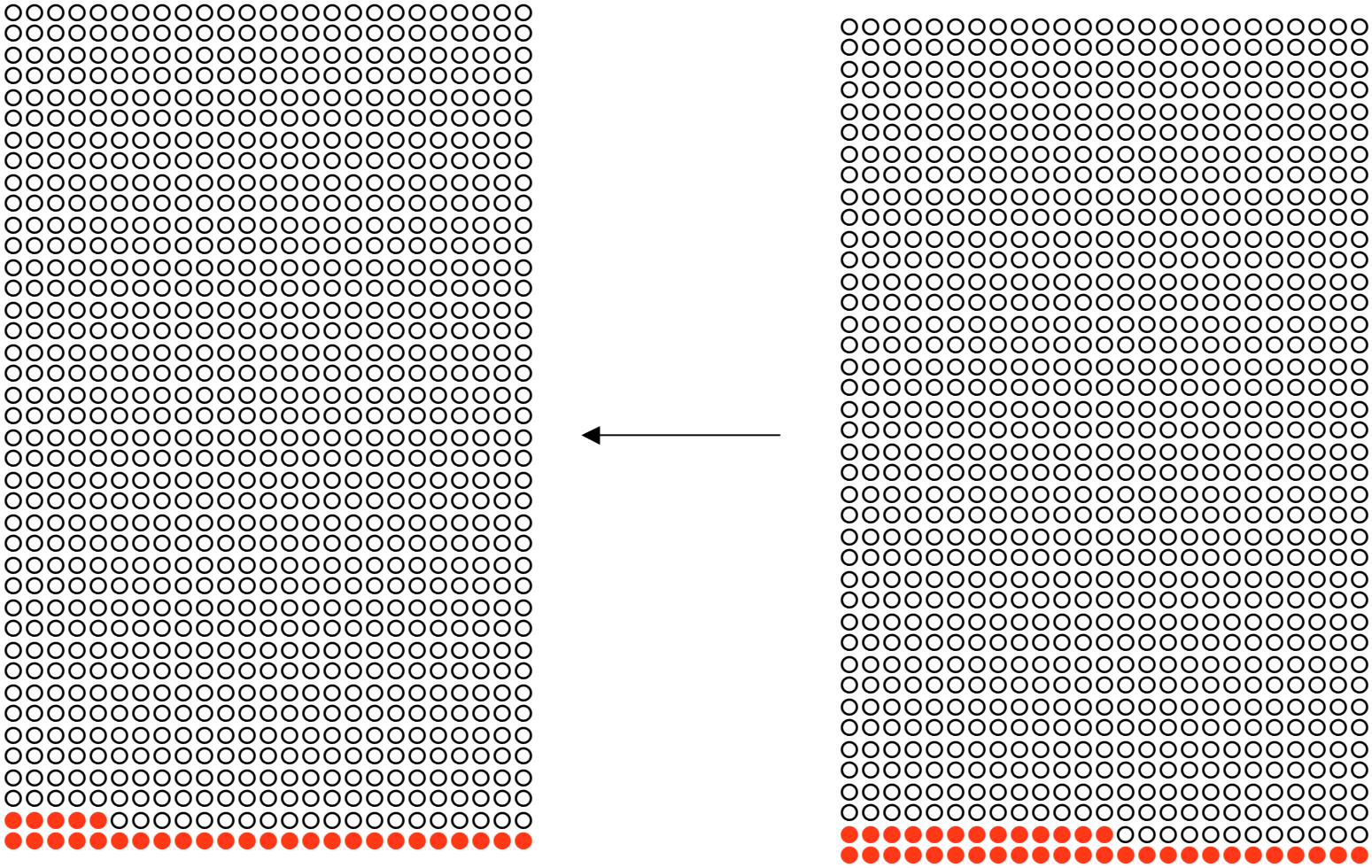
Treatment



50/1000
5%

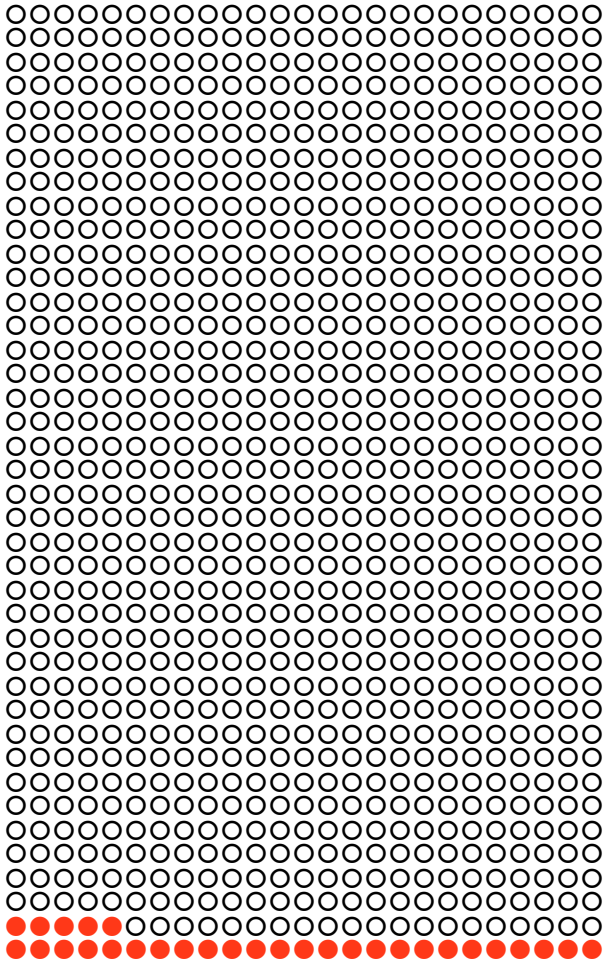
NNT 40

Risk reduction- relative (26%) or absolute (0.8%)?



What is the benefit of not taking HRT for 10 years regarding breast cancer incidence risk?

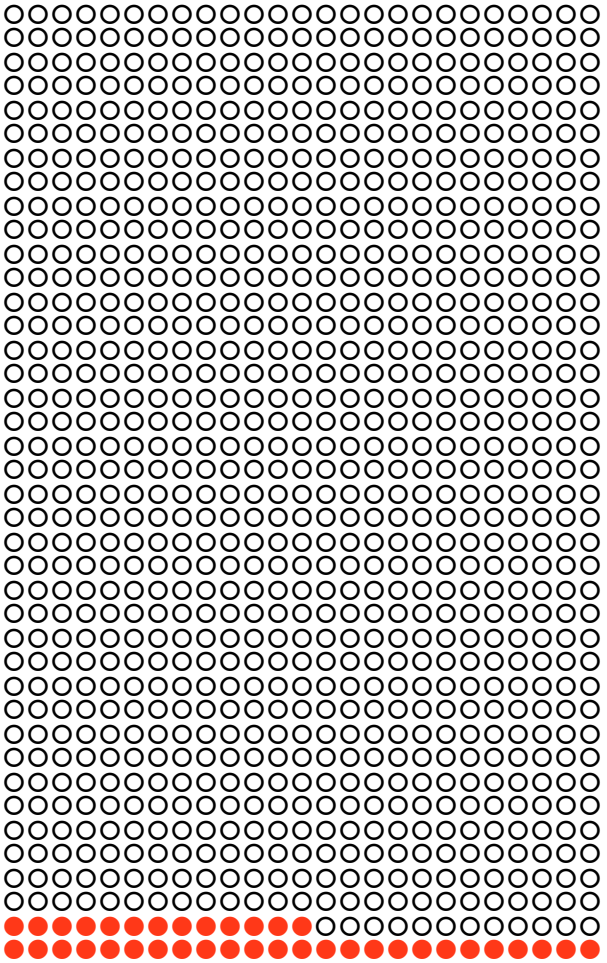
30/1000
3%



No HRT

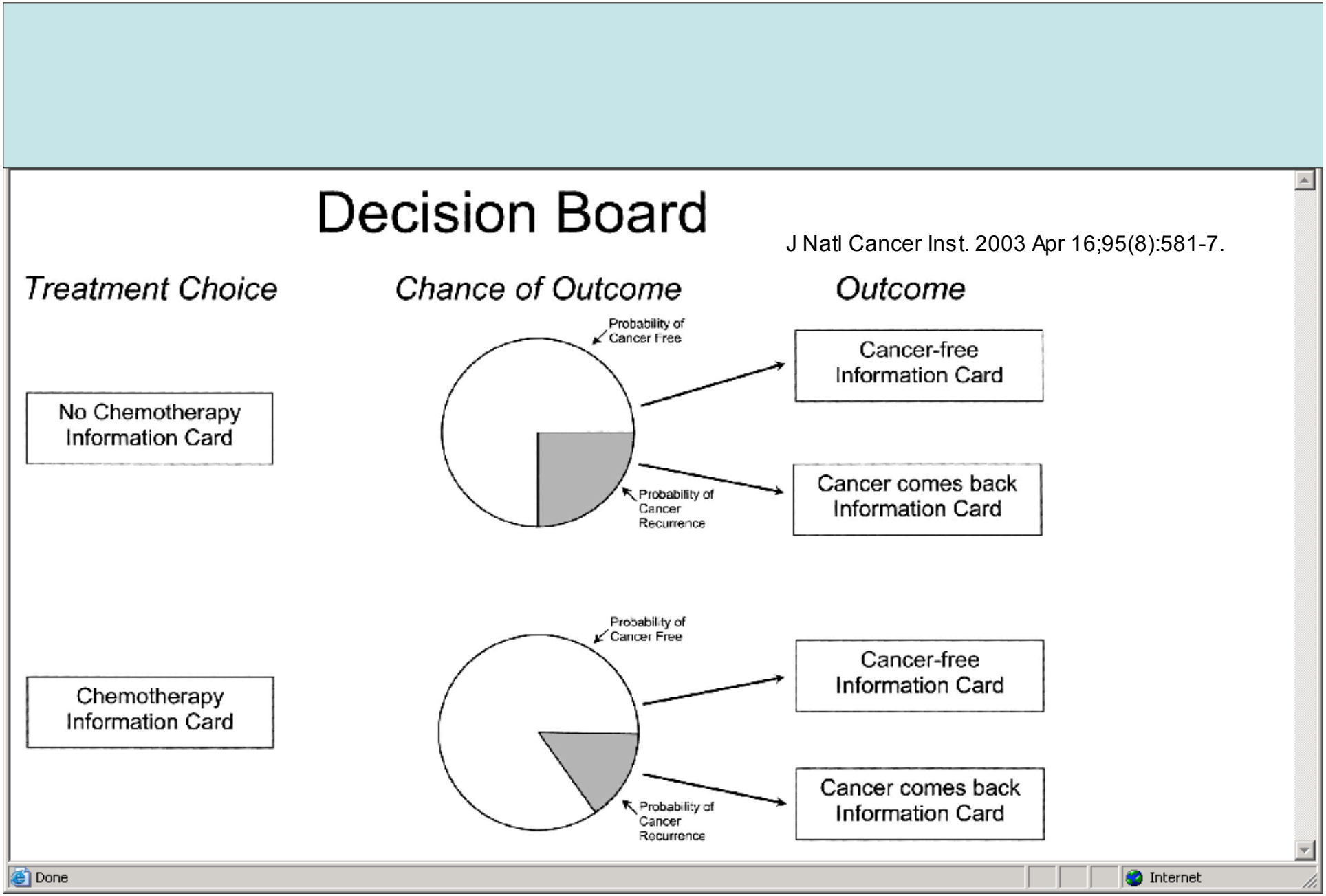
RRR 26%
ARR 0.8%
NNT 125

38/1000
3.8%



HRT for 10 years

Other graphical representations



- In men with no history of coronary artery disease, does lowering lipids result in reducing heart attacks and death?

Category: Cardiology **Type:** ☐ Case Control ☐ Cohort ☐ Meta-analysis ☑ RCT ☐ Systematic Review ☐ Other

Subcat: Hyperlipidemia

SubCat 2: Primary prevention

Quality:

Previous Record | Next Record | go to article

Question/ Condition: Are statins effective in primary prevention CHD in patients with average cholesterol and low HDL? AFCAPS/TexCAPs trial

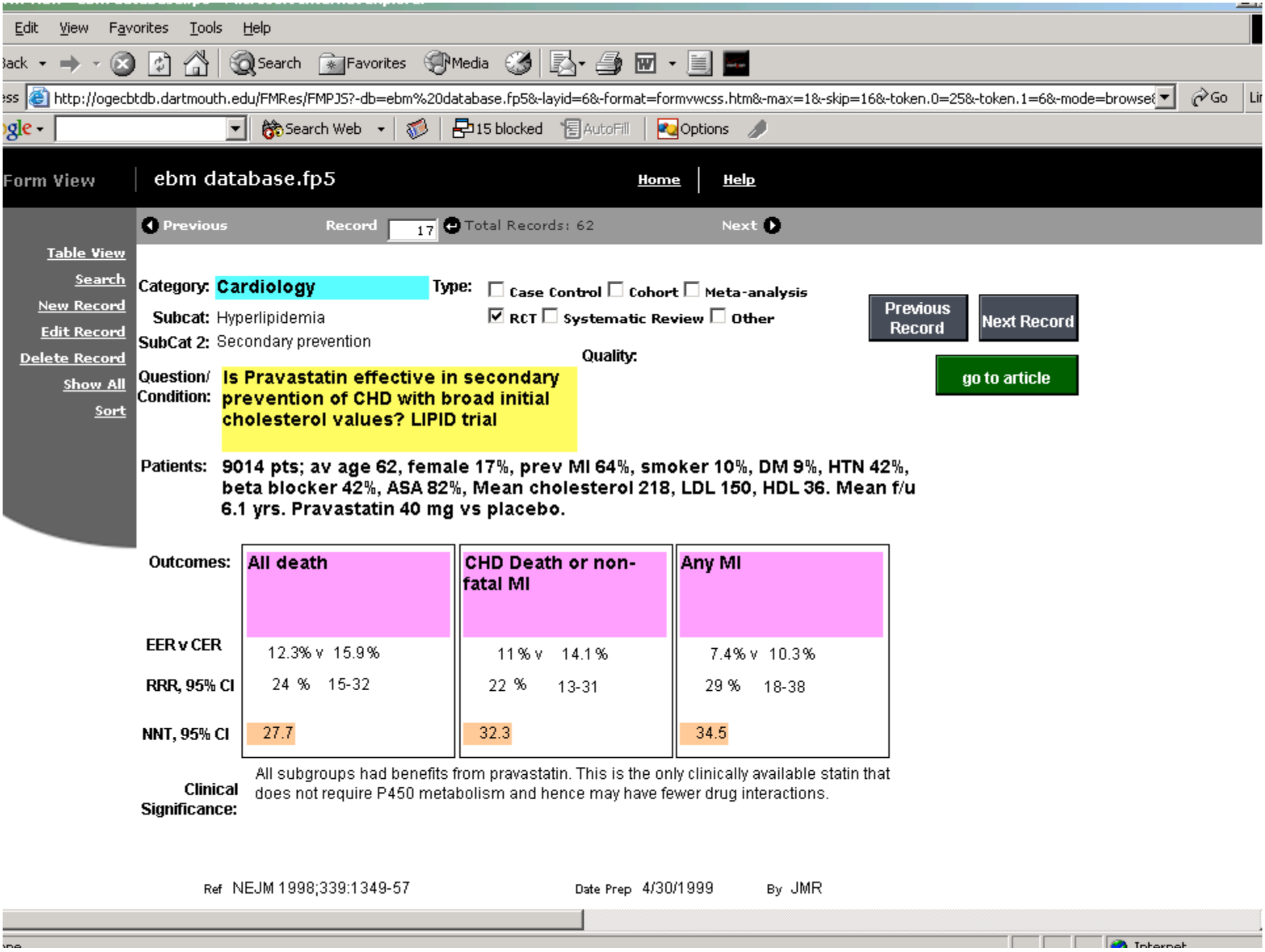
Patients: 6605; av age 58; 85% M; chol 180-264; HDL < 45 M,47F, f/u 5.2 years; composite outcome fatal/nonfatal MI, unstable angina, sudden cardiac death

Outcomes:	Acute event (fatal/nonfatal MI, USA, sudden cardiac death)		
EER v CER	4% v 6%	% v %	% v %
RRR, 95% CI	37 % 21to 50	%	%
NNT, 95% CI	50 33 to 97		

Clinical Significance: This establishes the legitimacy of using statins in primary prevention in men with the average cholesterol and low HDL syndromes- however, all cause mortality is not different.

Ref AFCAPS/TexCAPS JAMA 1998,279:1615-22 Date Prep 4/30/1999 By J. Ross

- In patients who have had a coronary event, does statin therapy reduce the risk of further events or death?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Category: Cardiology
Type: Case Control Cohort Meta-analysis RCT Systematic Review Other
Subcat: Hyperlipidemia
SubCat 2: Secondary prevention
Quality:
Previous Record
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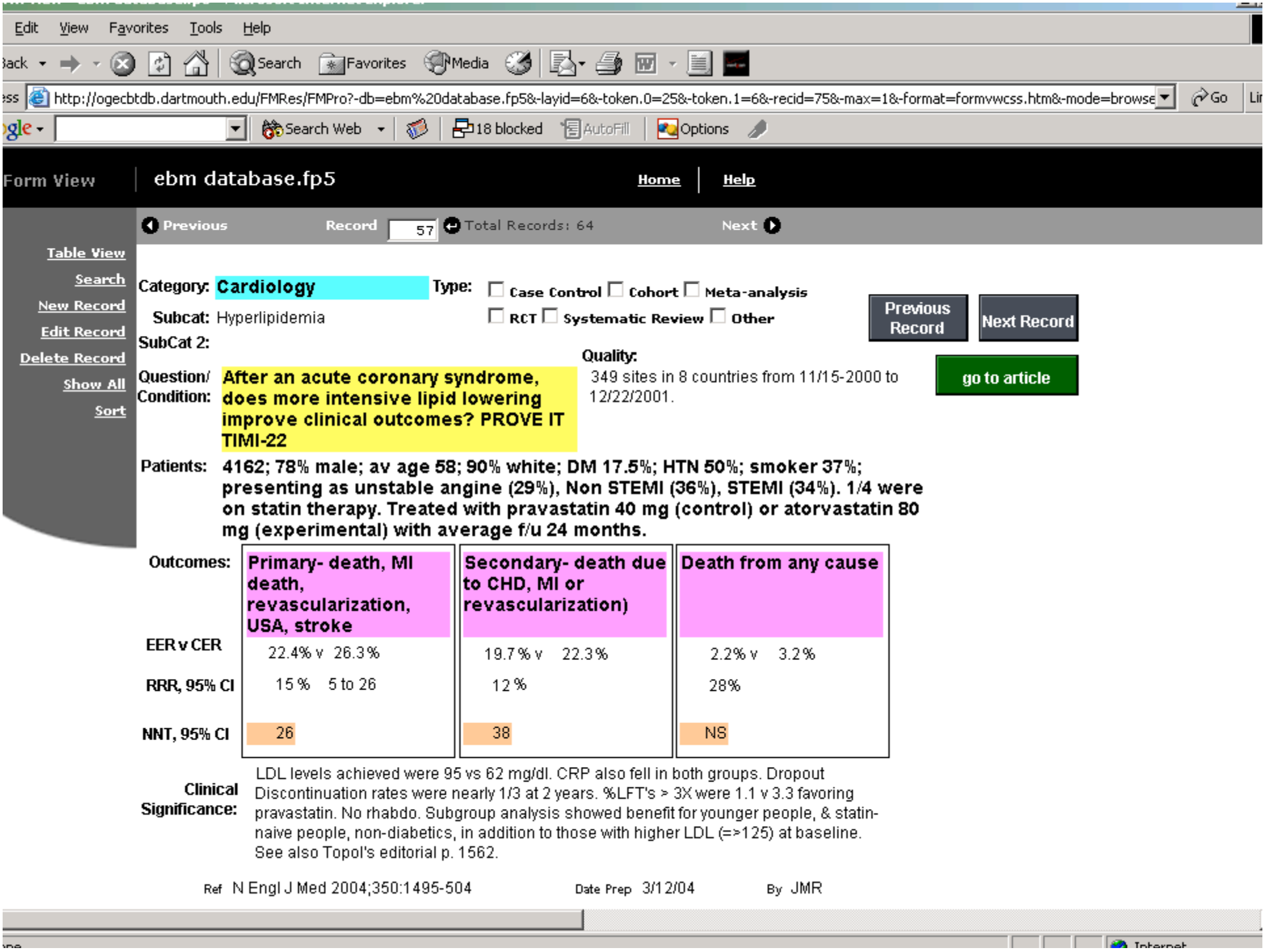
Question/ Condition: Is Pravastatin effective in secondary prevention of CHD with broad initial cholesterol values? LIPID trial
Patients: 9014 pts; av age 62, female 17%, prev MI 64%, smoker 10%, DM 9%, HTN 42%, beta blocker 42%, ASA 82%, Mean cholesterol 218, LDL 150, HDL 36. Mean f/u 6.1 yrs. Pravastatin 40 mg vs placebo.
Outcomes:
All death
CHD Death or non-fatal MI
Any MI
EER v CER
12.3% v 15.9%
11% v 14.1%
7.4% v 10.3%
RRR, 95% CI
24 % 15-32
22 % 13-31
29 % 18-38
NNT, 95% CI
27.7
32.3
34.5
Clinical Significance:
All subgroups had benefits from pravastatin. This is the only clinically available statin that does not require P450 metabolism and hence may have fewer drug interactions.
Ref NEJM 1998;339:1349-57
Date Prep 4/30/1999
By JMR

- In those who have had a coronary event, does very aggressive lipid lowering reduce the risk of further events and death?

Was that the Prove IT study?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Type: Case Control Cohort Meta-analysis RCT Systematic Review Other
Subcat: Hyperlipidemia
SubCat 2:
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Quality:
349 sites in 8 countries from 11/15-2000 to 12/22/2001.
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Question/ Condition: After an acute coronary syndrome, does more intensive lipid lowering improve clinical outcomes? PROVE IT TIMI-22
Patients: 4162; 78% male; av age 58; 90% white; DM 17.5%; HTN 50%; smoker 37%; presenting as unstable angine (29%), Non STEMI (36%), STEMI (34%). 1/4 were on statin therapy. Treated with pravastatin 40 mg (control) or atorvastatin 80 mg (experimental) with average f/u 24 months.
Outcomes:
Primary- death, MI death, revascularization, USA, stroke
Secondary- death due to CHD, MI or revascularization)
Death from any cause
EER v CER
22.4% v 26.3%
19.7% v 22.3%
2.2% v 3.2%
RRR, 95% CI
15% 5 to 26
12%
28%
NNT, 95% CI
26
38
NS
Clinical Significance:
LDL levels achieved were 95 vs 62 mg/dl. CRP also fell in both groups. Dropout Discontinuation rates were nearly 1/3 at 2 years. %LFT's > 3X were 1.1 v 3.3 favoring pravastatin. No rhabdo. Subgroup analysis showed benefit for younger people, & statin-naive people, non-diabetics, in addition to those with higher LDL (=>125) at baseline. See also Topol's editorial p. 1562.
Ref N Engl J Med 2004;350:1495-504
Date Prep 3/12/04
By JMR

- In patients with CHF who are on a diuretic, ACEI and digoxin, does spironolactone reduce the incidence of death?

  (RALES)

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Category: Cardiology **Type:** ☐ Case Control ☐ Cohort ☐ Meta-analysis ☑ RCT ☐ Systematic Review ☐ Other

Subcat: CHF

SubCat 2: Spironolactone

Quality:

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Question/ Condition: **Does Spironolactone in Class III/IV CHF improve survival? The RALES trial.**

Patients: **1663; av age 65; 73%M, Average BP 123/75, HR 81 and NYHA Class III 72%. Only 11% on beta blockers. Spironolactone 25-50 mg/day- 2 year follow-up**

Outcomes:	Death		
EER v CER	35% v 46%	% v %	% v %
RRR, 95% CI	30 % 18 to 40	%	%
NNT, 95% CI	8.8 7.2 to 11		

Clinical Significance: Impressive use of an old medication with surprisingly little hyperkalemia in patients. Note the low use of beta blockers.

Ref RALES NEJM 1999,341:709-17 Date Prep 2/2/00 By JMR

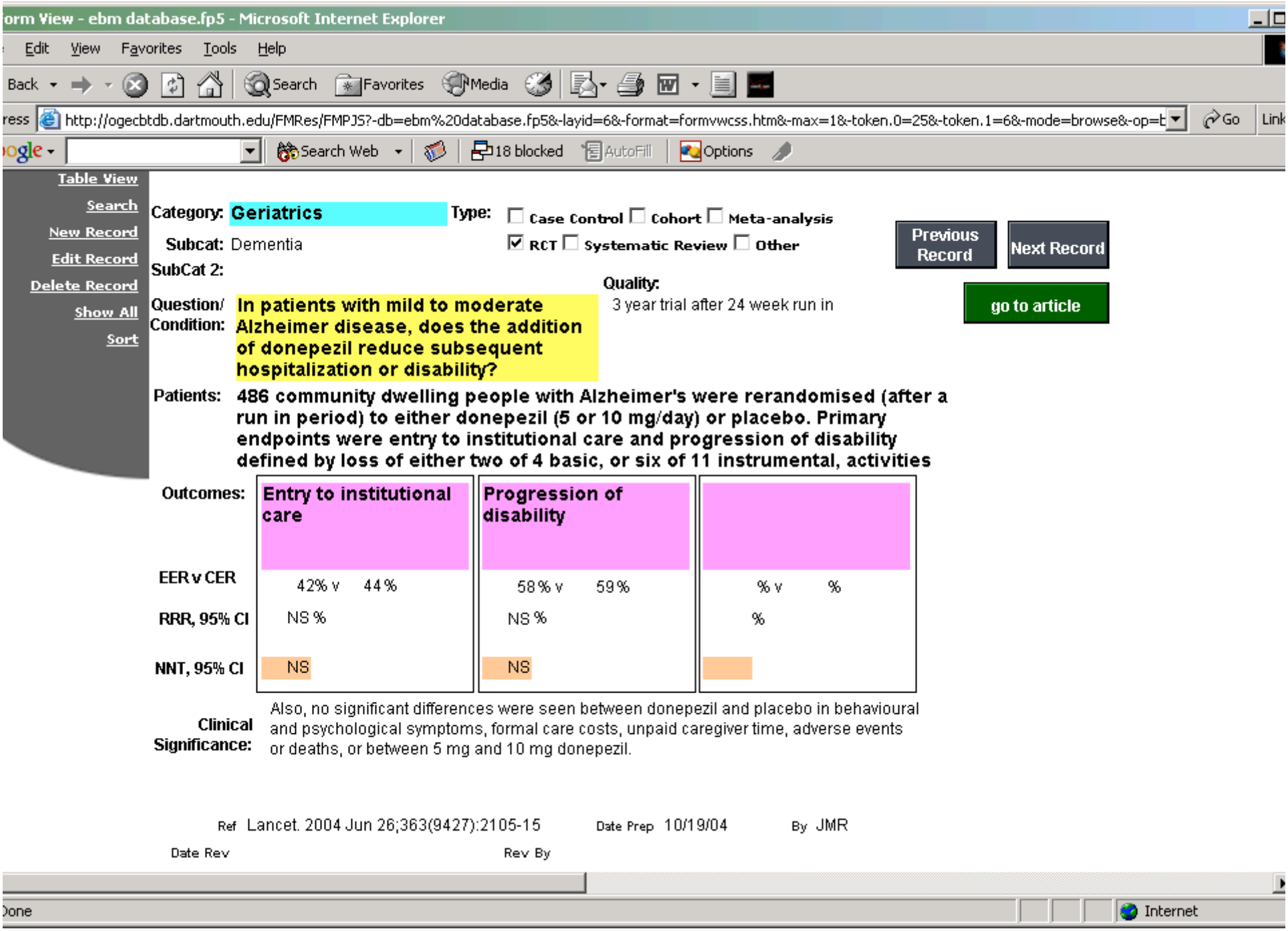
The spironolactone controversy

Juurlink *et al.* Rates of hyperkalemia after publication of the RALES. NEJM.2004;351:543

- Marked increase in patients with hyperkalemia admitted AFTER publication of RALES.
- Why?
  - Older
  - More diabetics and women
  - Higher doses
  - Higher use of beta blockers
- ***Patient selection!!!***

Juurlink *et al.*Rates of hyperkalemia after publication of the RALES. NEJM.2004;351:543

- In a patient with moderate Alzheimer's disease, does the cholinesterase inhibitor donepezil reduce the likelihood of institutional placement?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Type: Case Control Cohort Meta-analysis
Subcat: Dementia
RCT Systematic Review Other
SubCat 2:
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3 year trial after 24 week run in
go to article
Question/ Condition: In patients with mild to moderate Alzheimer disease, does the addition of donepezil reduce subsequent hospitalization or disability?
Patients: 486 community dwelling people with Alzheimer's were rerandomised (after a run in period) to either donepezil (5 or 10 mg/day) or placebo. Primary endpoints were entry to institutional care and progression of disability defined by loss of either two of 4 basic, or six of 11 instrumental, activities
Outcomes:
Entry to institutional care
Progression of disability
EER v CER
42% v 44%
58% v 59%
% v %
RRR, 95% CI
NS %
NS %
%
NNT, 95% CI
NS
NS
Clinical Significance: Also, no significant differences were seen between donepezil and placebo in behavioural and psychological symptoms, formal care costs, unpaid caregiver time, adverse events or deaths, or between 5 mg and 10 mg donepezil.
Ref Lancet. 2004 Jun 26;363(9427):2105-15
Date Prep 10/19/04
By JMR
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Let's think about this…

- It is important to know (or gain access) to the evidence
  - Benefits, harms, costs, competing needs
- Patient selection is critical
- It is a challenge to pick a method for communicating risks
  - RRR, ARR, NNT/t, graphic aids
- It is an evolving art
  - How to assess patient values?
  - How to assess comprehension?

Now let's practice…

- You have a patient with COPD who hears that treatment X may be helpful
  - Have a discussion regarding risks and benefits
- You have a patient whose family requests treatment with Aricept (donepezil).
  - Have a conversation with your patient (or family) regarding your recommendation

Putting evidence based medicine into practice

- What do you want to do differently in the future?
- What do you need to accomplish this?