

*“CLINICAL TRIALS, DO THEY ADDRESS THE REAL WORLD OR MY PATIENT ?”*  
*“CLINICAL TRIALS (EFFICACY) AND THE REAL WORLD (EFFECTIVENESS)”*

## **-Introductory Background**

Definition - EBM, Phases, Progress, Megatrials

## **- Exclusion / Inclusion - Bias**

Industry, Journals, Low Recruitment

Sex, Elderly, Race, Developing Countries

## **-Registration**

Negative Trial, Phase 1, Report - Harm

## **- Consent - Bias**

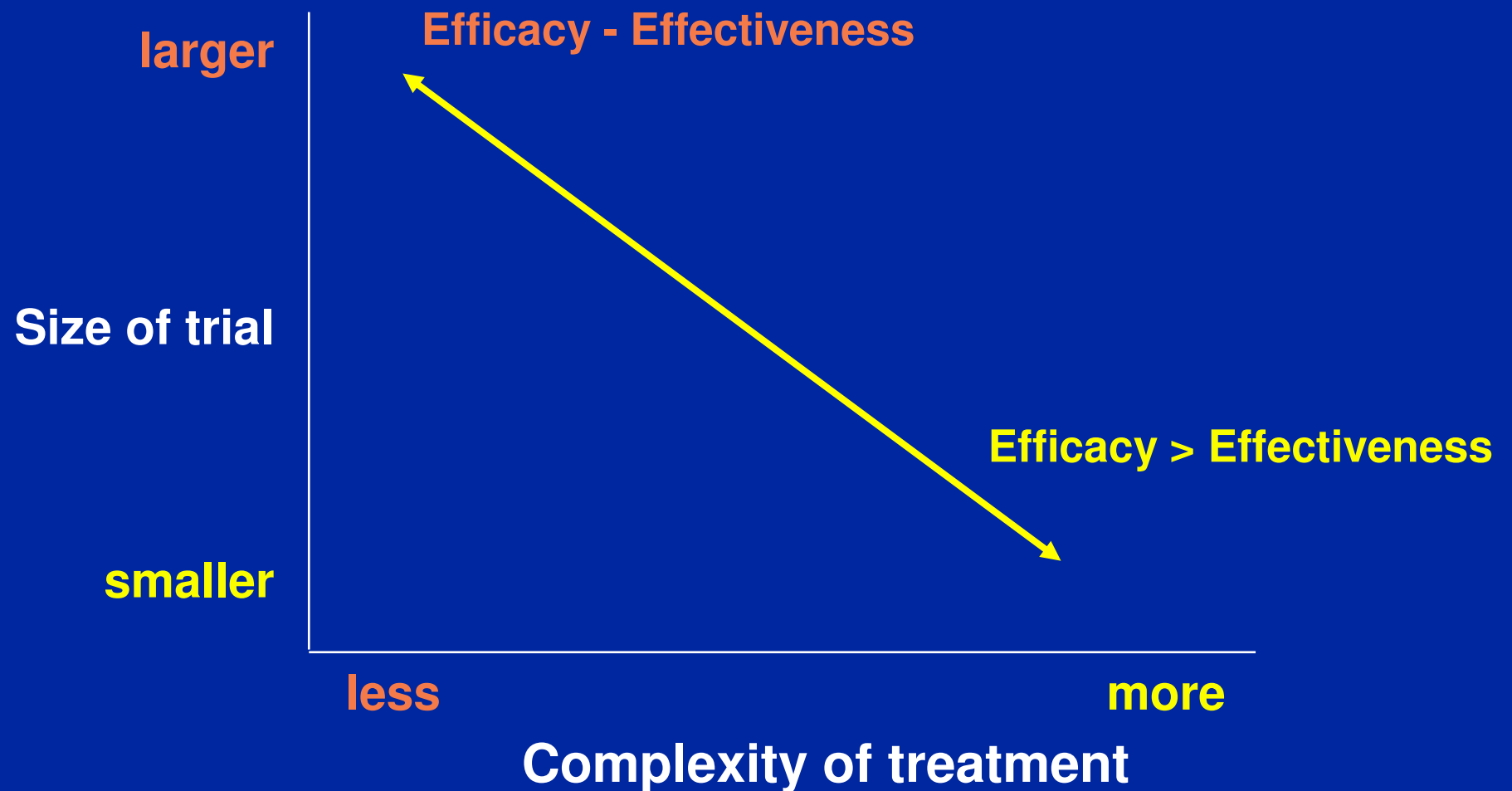
## **- Statistical Methodology**

Double-Blind, Open Label, Non Inferiority, Early Stop,

Subgroups, Observational / Registry, Surrogate End-Points,

## **-Trials or EBM vs the Individual Patient**

# 1) PROPOSED FRAMEWORK FOR GENERALIZING THE RESULTS OF A RANDOMIZED CLINICAL TRIAL



## 2) Clinical Trials: Lemons, Oranges, and Complexity

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**Spiraling Costs** Threaten Gridlock

The Promise and Pitfalls of Clinical Trials **Overseas**

Making Clinical **Data Widely Available**

**Women** Abound in NIH trials

E Marshall. Science **2008**; 322:209

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## 3) Guidelines & Statements of the AHA 2009 - V Fuster Edit

**“Just a Roadmap, not a Policy”**

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A clinical trial is defined as a “prospective scientific experiment that involves human subjects in whom treatment is initiated for the evaluation of a therapeutic intervention”. Nothing more clearly indicates the key role of an RCT in modern clinical research than the placement of this **specific research method at the top of the list of levels of evidence in evidence-based medicine (EBM)**.

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K Stanley. Circ **2007**; 115:1164 (Harvard SPH)

# Definition, EBM, Phases, Progress, Megatrials

Phase	No. of Patients	Length of Phase	Goal
1	20-100	Several months	Safety, dosages, and efficacy ?
2	100-500	Several months to 2 years	Effectiveness ? and short-term safety
3	500-3000	1-4 Years	Safety & Effectiveness
4	> 3000	Ongoing	Long-term safety and rare adverse effects

J Khandekar et al., Arch Intern Med 2006; 166:1440 (Evanston,IL)

## **Definition - EBM, Phases, Progress, Megatrials** **1). Drug Development, time, effort, and money.**

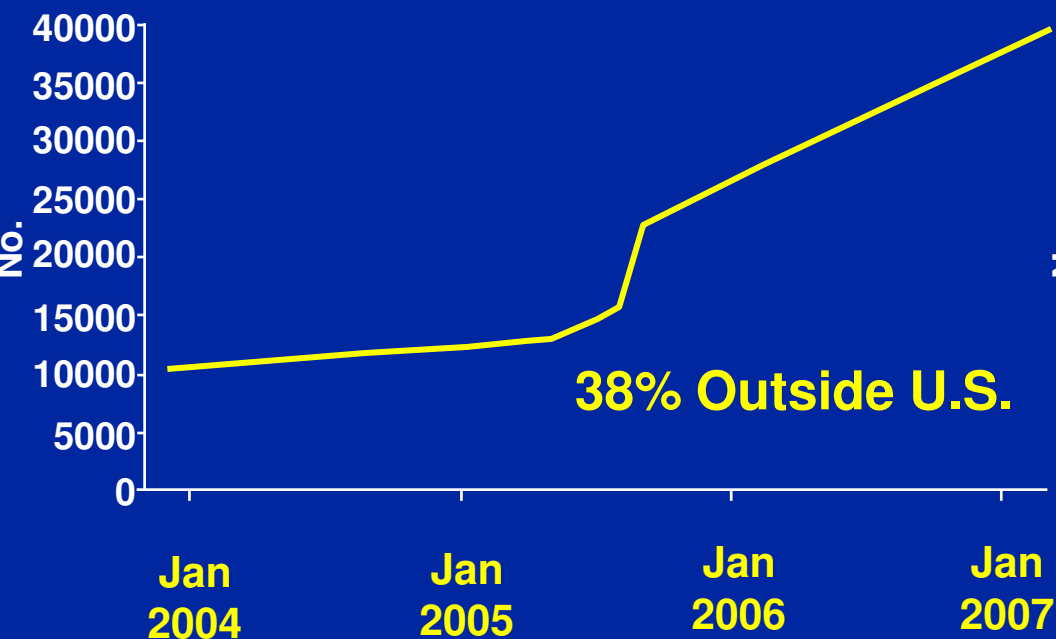
**It is estimated that of approximately 10,000 drugs** considered promising in the initial screening assay results, fewer than **10** make it to a clinical trial, and **only 2** are eventually approved by the FDA. The importance of the fourth phase of testing has recently been emphasized by the identification of new toxic effects of selective cyclooxygenase-2 inhibitors.

J Khandekar et al., Arch Int Med **2006**;166:1440 (Evanston)

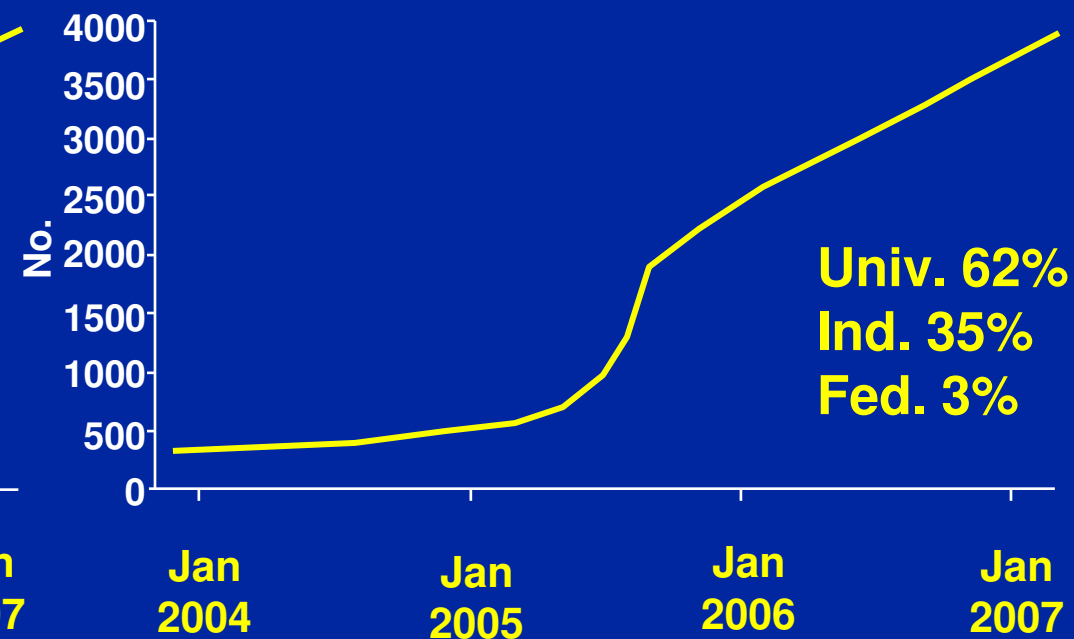
# Definition - EBM, Phases, Progress, Megatrials

## 2). Number of Clinical Trials.gov since Jan 2004

### Records



### Organizational Accounts



# Definition - EBM, Phases, Progress, Megatrials

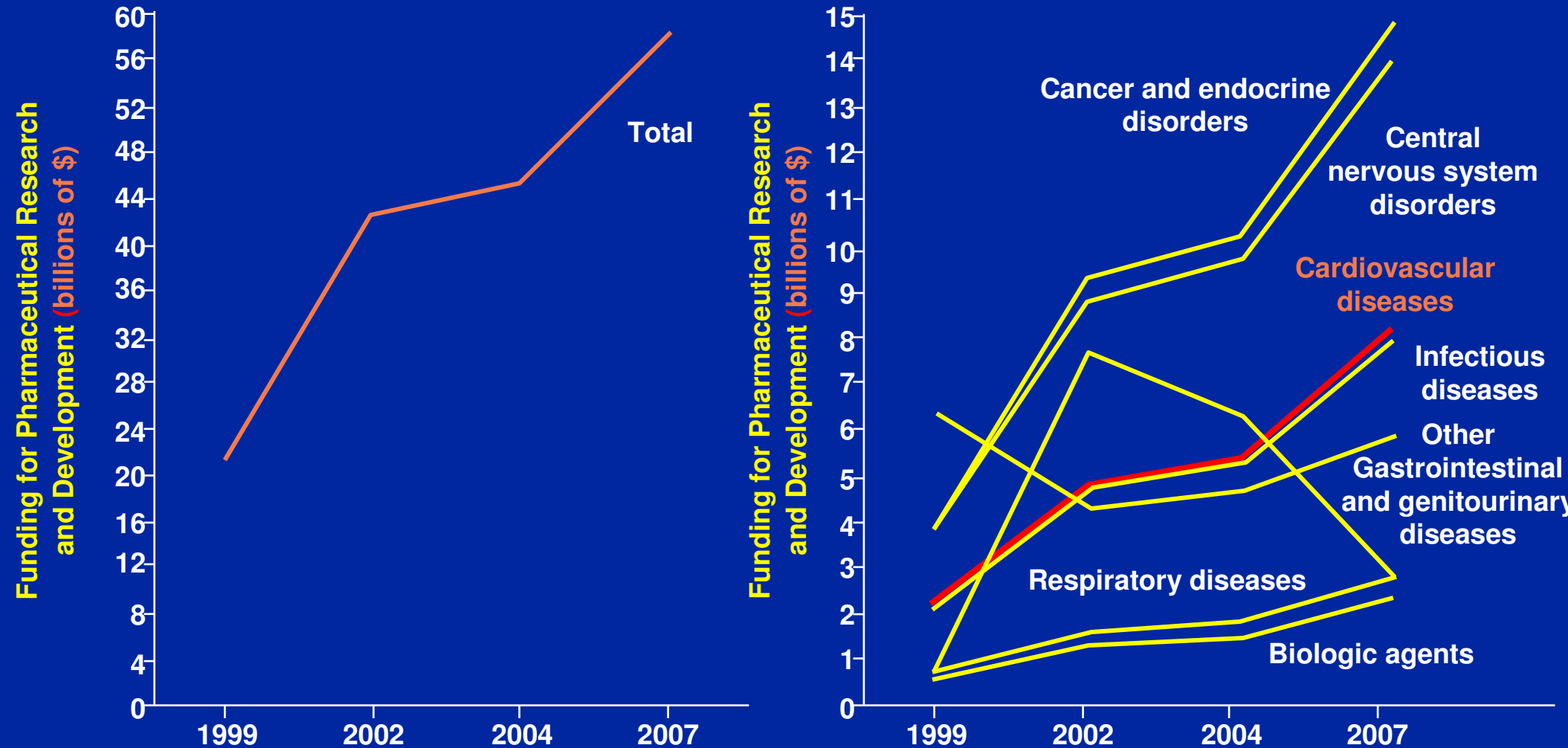
## 2) Clinical Trial Registration

In April 2007, the registry contained over 40,000 trials, with more than 200 new trial registrations occurring weekly. The 4 other registries that meet the ICMJE criteria have also grown as scores of journals have adopted the ICMJE clinical trials registration policy.<sup>3</sup> Fortunately, the **WHO's International Clinical Trial Registry Platform (ICTRP)**, which was nascent when the ICMJE began trial registration, has matured rapidly and provides options for those who desire a wider array of registries.<sup>3</sup>

1. AW Chau. JAMA 2004;291:2457 - 2. ICMJE (C DeAngelis) NEJM 2004; 351:1250
3. ICMJE (C Laine) JAMA 2007; 298:43 - 4. DA Zarin . JAMA 2007; 297:2112

# Definition - EBM, Phases, Progress, Megatrials

## 3). Worldwide Funding for Pharmaceutical R&D



Thomson CenterWatch. Companies that are members of the Pharmaceutical Research and Manufacturers of America. Data for 2007 are projections.  
 R Steinbrook. N Engl J Med 2005; 353:1091

# Definition - EBM, Phases, Progress, Megatrials From Streptomycin to the era of Megatrials

RCTs assessing serious outcomes in CV disease have grown with 'megatrials' becoming more common with the realization that wrong conclusions resulted from random error in inadequately sized trials. Simple design and a heterogeneous patient population were early features. Study supervision is then in the hands of an independent steering committee. Prospectively defined interaction with the sponsor facilitates unbiased design and conduct. The patient is protected by a data safety monitoring board. Mega-trials are under threat from over-regulation, costs, and difficulties in execution.

## Definition - EBM, Phases, Progress, Megatrials Era of Megatrials, Marginal Benefit and Bias

Although we as a society continue to have much to gain from a well-conducted and fairly interpreted trials, **we also have much to lose from one that is flawed, overinterpreted, or distorted in message.**

J Loscalzo. Circulation **2005**; 112:3026

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## Exclusion / Inclusion in RCTs

### 1). Scholarly Articles About Seeding Trials\*

Study, Year	Article Type
Kessler et al., 1994	Editorial
Stephens, 2003	Editorial
Fretheim and Oxman, 2005	Cross-sectional survey
Psaty and Rennie, 2005	Editorial
Andersen et al., 2006	Observation cohort
Greenland and Lloyd-Jones, 2008	Editorial
Hill et al., 2008	Review

\* **Clinical studies conducted by pharmaceutical companies that are designed to seem as if they answer a scientific question but primarily fulfill marketing objectives**

KP Hill et al., Ann Int Med 2008; 149:1

## Exclusion / Inclusion in RCTs - Bias

### 1). Scholarly Articles About Seeding Trials\*

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The design and conduct of drug treatment trials **remain primarily in the hands of industry. Public funding** to prioritize, plan, and conduct major drug safety and efficacy studies of public health importance **is not likely to replace the current system soon.** While transparency is a critical preventive measure, **bias is not identifiable by the fact that funding may have been received from a source with special interests.**

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BM Psaty. JAMA **2009**; 301:1477 (Seattle)

## Exclusion / Inclusion in RCTs - Bias

### 1). Scholarly Articles About Seeding Trials

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Prior work indicates that therapeutic trials funded by for-profit organizations are more likely to report positive findings than trials funded by not-for-profit organizations. What impact, if any, funding source has on subsequent dissemination of trial data is uncertain. We assessed 303 consecutive superiority trials of cardiovascular medicine published between January 1, 2000, and July 30, 2005, in the *Journal of the American Medical Association*, *The Lancet*, and the *New England Journal of Medicine*. Higher citation rates were observed for industry-funded trials than for federally funded trials even when the trials dealt with similar issues and were published back-to-back in the same journal. Dissemination of clinical trial results is important for clinical practice but appears to be biased in favor of for-profit entities. .

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D Conen, J Torres, PM Ridker. *Circ* 2008; 118:1321 (Boston)

## Exclusion / Inclusion in RCTs - Bias

### 2). Published in High-Impact General Medical Journals

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The MEDLINE database was searched for RCTs published between 1994 and 2006 in **high impact general medical journals**; 283 were selected using a series technique. **Common medical conditions** formed the basis for exclusion in **81%** of trials. Patients were excluded due to **age** in **72%** of all trials (60% in pediatric populations and 38% in older adults). Individuals receiving **commonly prescribed medications** were excluded in **54%** of trials. **Conditions related to female sex** were grounds for exclusion in **39%** of trials. **Of all exclusion criteria, only 47.2% were graded as strongly justified in the context of the specific RCT.**

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## Exclusion / Inclusion in RCTs - Bias

### 3). Low Recruitment

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This is a self-report **survey of 400 patients** who underwent general medical evaluations between September and November 2006 at a tertiary care **academic medical center in Rochester, MN**. We measured knowledge of access to clinical trials, attitudes toward participation, recruitment preferences, and beliefs about research integrity.

**Patients are interested in participating in clinical trials but commonly lack adequate information.** If patients received more information (through their treating physicians), enrollment might improve.

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A Sood et al., Mayo Clin Proc **2009**; 84:243

## Exclusion / Inclusion in RCTs - Bias

### 3). Low Recruitment

Patients are usually recruited on the basis of stringent inclusion and exclusion criteria that are often worryingly dissimilar to the overall patient population. According to the analysis carried out by Brett and colleagues, **many CRTs included markedly less than 10% of all screened patients.**

If the majority of patients are excluded from participating in RCTs on the basis that they cannot undergo equivalent interventional treatment, it follows that the study results and conclusions are **exclusively valid for patients with identical inclusion criteria as those in RCTs.**

MTR Grapow et al Jnl Thorac Cardiovasc Surg **2006**;132:5

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# Sex, Elderly, Race/Ethnicity, Developing Countries Ignored Issue

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Cardiovascular disease (CVD) is the **most common cause of death in American women** and accounts for a full one-third of all deaths. Although the common perception may be that CVD affects mainly men, there is equal prevalence of this disease between **the genders by the age of 40**, and **by the age of 60 more women than men are affected**. More women than men have died from CVD causes on a yearly basis since the mid 1980s, and **whereas the CVD mortality has steadily declined in men over the past 30 years**, it has remained steady in women until very recently when CVD mortality was noted to decrease for both genders.

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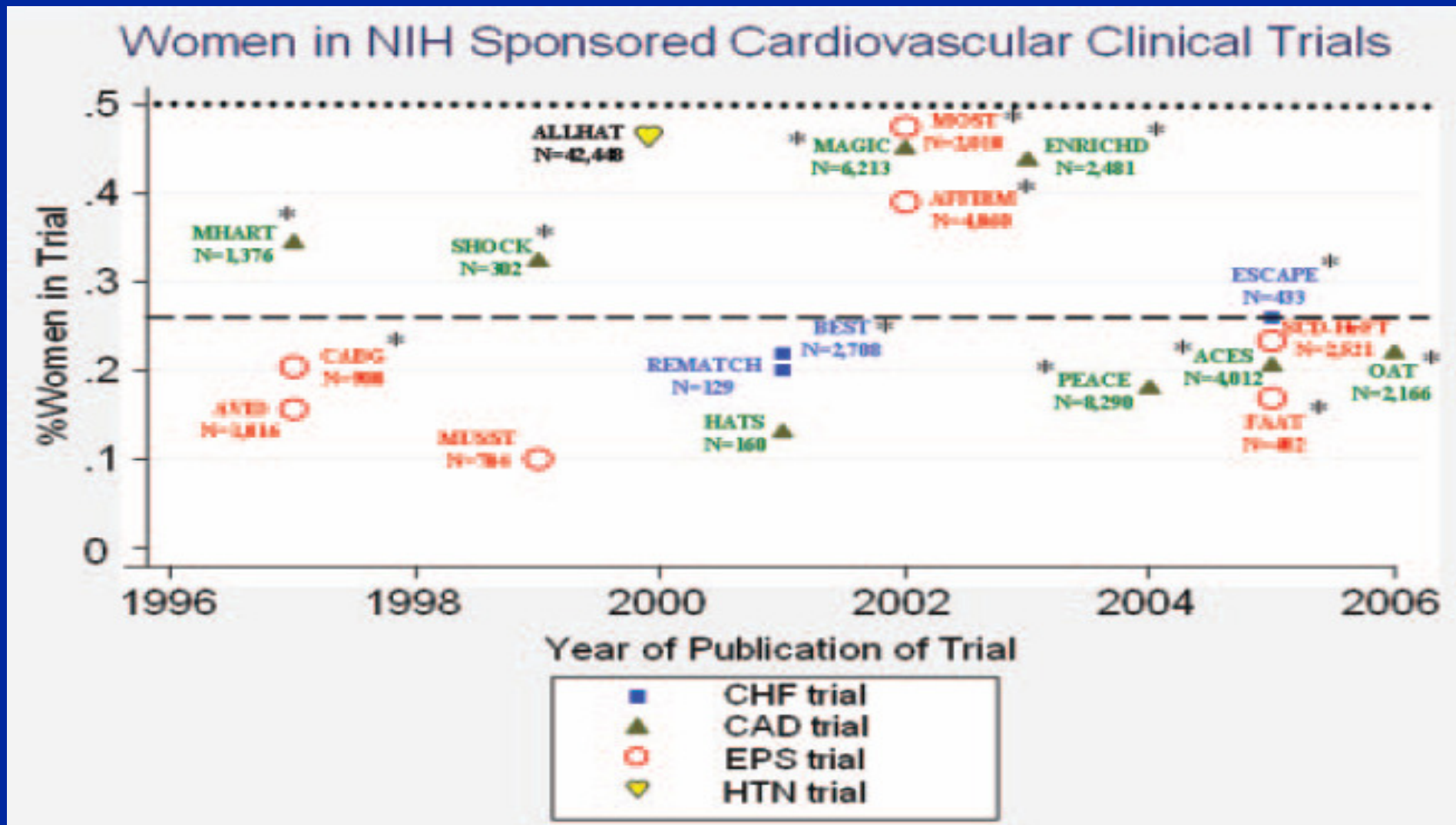
ESH Kim, V Menon. ATVB **2009**; 29:279 (Cleveland)

**COMPARISON OF THE MEAN PROPORTION OF WOMEN IN NHLBI SPONSORED PHASE 3-4 CV CONTROLLED TRIALS (1997-2006) TO PROPORTION OF WOMEN AMONG THE GENERAL POPULATION WITH CV DISEASE**

<b>Disease Type</b>	<b>% Women (mean)</b>	<b>% Women Among Those With Disease</b>	<b>Source</b>
<b>Coronary Artery Disease</b>	<b>29%</b>	<b>46%</b>	<b>AHA</b>
<b>Congestive Heart Failure</b>	<b>23%</b>	<b>52%</b> <b>60%</b> <b>50%</b>	<b>ADHERE</b> <b>NHFP</b> <b>AHA</b>
<b>Sudden Cardiac Death</b>	<b>17%</b>	<b>23%</b> <b>16%</b> <b>32%</b>	<b>AVID registry</b> <b>MUSTT registry</b> <b>Seattle/King EMS</b>
<b>Atrial Fibrillation</b>	<b>39%</b>	<b>55%</b>	<b>AHA</b>
<b>Hypertension</b>	<b>47%</b>	<b>53%</b>	<b>AHA</b>
<b>Cardiovascular Disease</b>	<b>27%</b>	<b>53%</b>	<b>AHA</b>

**ESH Kim, V Menon. ATVB 2009; 29:279 (Cleveland)**

# Status of Women in Cardiovascular Clinical Trials



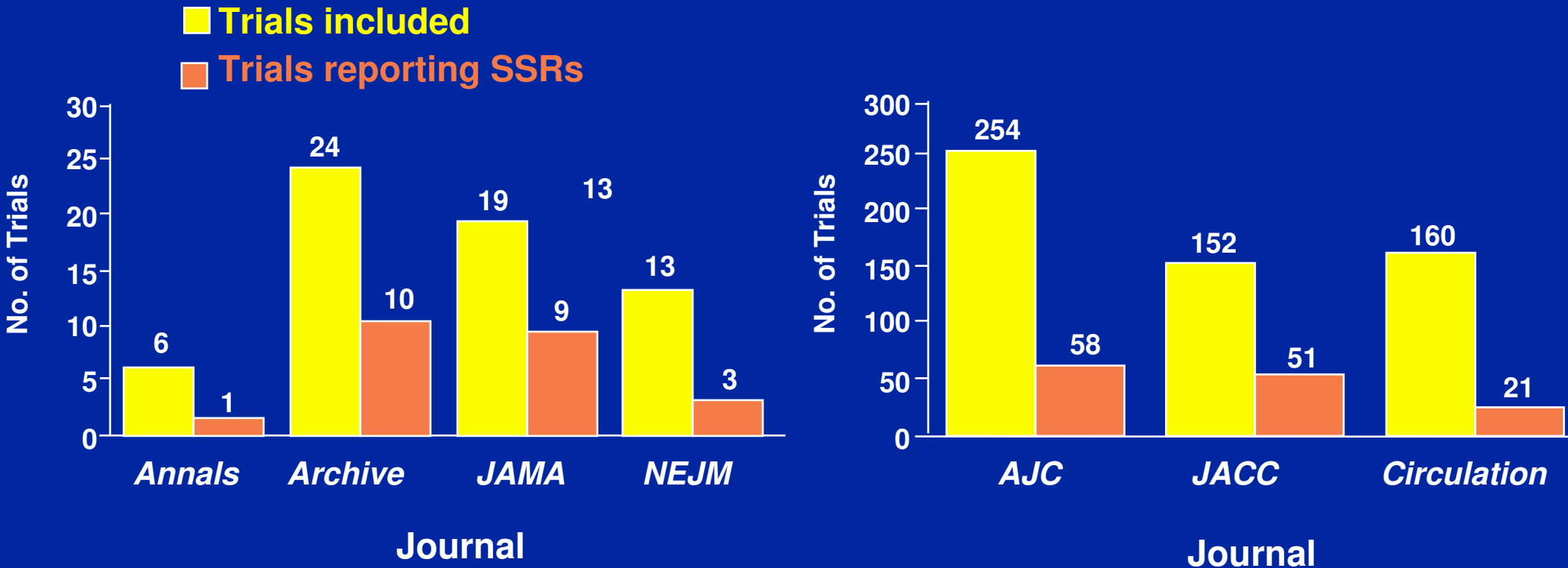
ESH Kim et. al. *ATVB*. 2009;29:279.

\* Gender Analyses Published (13/19)

C Kim et. al. *JACC* 2009;52:672.

# Sex, Elderly, Race/Ethnicity, Developing Countries

## Sex Specific Results (SSR) Report in Journals



# Sex, Elderly, Race/Ethnicity, Developing Countries An Urgent Need

Considerable challenges are associated with conducting randomized, controlled trials successfully in special patient populations such as the elderly.

**Chronologic age per se should not be a valid criterion for exclusion, and for this reason, most clinical trials do not set an upper age limit.**

**Ageism . Many physicians and patients have an innate bias that associates older age with inferior outcomes. Unless these concerns are substantiated by rigorous data, they do not advance science in any way that enhances patient care.**

## **Sex, Elderly, Race/Ethnicity, Developing Countries** **Cautious Approach**

The recently completed African-American Heart Failure Trial or **A-HeFT** and the African American Study of Kidney Disease and Hypertension or **AASK**, are **examples of studies focused in ethnic minorities that demonstrate the value of this research.**

The more than 40000 participant Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial or **ALLHAT** is an example of a clinical trial designed to prospectively assess ethnic differences in response to antihypertensive therapy. **However, all major classes of drugs work in all ethnic groups, albeit with minor differences in adverse or blunted responses.**

## Sex, Elderly, Race/Ethnic, Developing Countries Ethical Issues

Trials are often **much cheaper** to do in countries where salaries and the cost of living is fairly low. Developing countries can offer “**treatment naïve**” in patients who **have had fairly low exposure to other drugs**. In such countries, “volunteers” are **often easier to recruit**

**Investigative journalism** may often fall into the trap of **oversimplifying**, but this does not diminish its importance in **sensitising public attitudes and catalysing an appropriate response** (John Le Carré’s, “*The Constant Gardener*”, Sonia Shah’s, “*The Body Hunters: Testing New Drugs on the World’s Poorest Patients*”).

Lancet **2006**; 368:1761

# Sex, Elderly, Race/Ethnic, Developing Countries Ethical Issues

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The increasing globalization of clinical research trials  
calls for **more effective ethical and legal rules to protect  
both research subjects and scientific integrity.**

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GJ Annas. NEJM **2009**; 360:20 (Boston Univ. SPH)

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# Clinical Trial Registration

## Negative Trial , Phase 1, Report - Harm

In April 2007, the registry contained over 40,000 trials, with more than 200 new trial registrations occurring weekly. The 4 other registries that meet the ICMJE criteria have also grown as scores of journals have adopted the ICMJE clinical trials registration policy.<sup>3</sup> Fortunately, the WHO's International Clinical Trial Registry Platform (ICTRP), which was nascent when the ICMJE began trial registration, has matured rapidly and provides options for those who desire a wider array of registries.<sup>3</sup>

1. AW Chau. JAMA 2004;291:2457 - 2. ICMJE (C DeAngelis) NEJM 2004; 351:1250
3. ICMJE (C Laine) JAMA 2007; 298:43 - 4. DA Zarin . JAMA 2007; 297:2112

# Clinical Trial Registration

## Negative Trial , Phase 1, Report - Harm

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In Section 801 of the **FDA Amendments Act**, enacted in **September 2007**, Congress expanded the requirements for sponsors and investigators to post information about clinical trials, including selected aspects of trial results, on the U.S. government Web site [ClinicalTrials.gov](http://ClinicalTrials.gov). The dedication of patients who take the risks to participate in clinical research is **dishonored when their data remain secret**.

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AJJ Wood. NEJM **2009**; 360:8

## Clinical Trial Registration Negative Trial , Phase 1, Report - Harm

Researchers (and journals) typically are **less excited** about trials that show that a new treatment is inferior to standard treatment (negative trials).<sup>2</sup>

Since July 2005 the ICMJE member journals required, as a condition of consideration for **publication and with an incentive for quality, registration in a public trials registry** before the patient enrollment<sup>2</sup>.

1. AW Chau. JAMA **2004**;291:2457 - 2. ICMJE (C DeAngelis) NEJM **2004**; 351:1250
3. ICMJE (C Laine) JAMA **2007**; 298:43 - 4. DA Zarin . JAMA **2007**; 297:2112

# Clinical Trial Registration

## Negative Trial , Phase 1, Report - Harm

The **ICMJE** is expanding the definition of the types of trials that must be registered to **include those preliminary phase 1 trials -pharmacokinetics, major toxicity-** and adopts the **WHO's definition** of clinical trial: “any research study that prospectively assigns human participants or groups of humans to one or more health-related interventions to evaluate the effects on health outcomes”. **The ICMJE member journals started to implement the expanded definition of ethically directive trials for trials that began enrollment on or after July 1.<sup>3</sup>**

1. AW Chau. JAMA **2004**;291:2457 - 2. ICMJE (C DeAngelis) NEJM **2004**; 351:1250
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# Clinical Trial Registration

## Negative Trial , Phase 1, Report - Harm

**a)** In response to poor-quality reporting of RCTs, many medical journals and editorial groups have now endorsed the **CONSORT** (Consolidated Standards of Reporting Trials) statement, a 22-item checklist and flow diagram. Because **CONSORT** primarily aimed at improving the quality of reporting or efficacy, only 1 checklist item specifically addressed the reporting of safety. **The result is the standard CONSORT checklist with 10 new recommendations about reporting early harms-related issues**, accompanying explanation, and examples to highlight specific aspects of proper reporting.

**CONSORT** (JPA Ioannidis et al.) Ann Intern Med **2004**; 141:781

# Clinical Trial Registration

## Negative Trial , Phase 1, Report - Harm

**b)** For commonly used medications, even a slight increase in the risk of serious harmful CV events may be clinically relevant. The problem is that RCTs are typically grossly underpowered to estimate such risks. Therefore, meta-analyses of several RCTs are a viable option. Cochrane database showed that 138 systematic reviews had performed meta-analyses on at least 4,000 randomized patients, but only 18% of those addressed at least one type of harm, whereas 26% had limited or nonspecific data on harms, and 56% had no harms data at all. An extension of the CONSORT statement for harms provides explicit guidance on how to improve reporting.

AV Hernandez et al., Am Heart J 2008; 156:23

ME Farkough, V Fuster. Nature Cardio Med 2007; 4:2007

## Clinical Trial Registration

### Negative Trial , Phase 1, Report – Harm (Phase 4)

**c).** As the pace of development in medical technology accelerates, **breakthrough technologies will continue to pose unanticipated safety issues for patients and clinicians or late technovigilance.** Recommended approaches to dealing with these pitfalls are to consider creative study design strategies that link pre- and postmarket data, **declare postmarket surveillance a public health issue,** direct research funding to this endeavor, and involve centers with research experience in the process.

## Clinical Trial Registration

### Negative Trial , Phase 1, Report – Harm (Phase 4)

d). To address important long term public health questions, such as the so called **late pharmacovigilance**, as the FDA is contemplating for antidiabetic therapy. **With the Reagan Udall Foundation, the FDA Amendments Act** has provided a potential mechanism for design, conduct, and funding of selected studies. **When an important drug safety question arises, the FDA can put out a request for proposals through the foundation, with industry funding**

BM Psaty et al., JAMA **2008**; 300:952 (Seattle, Leiden)

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## *CONSENT BIAS IN RESEARCH*

Consent bias, also known as authorisation bias or volunteer bias, **it describes the impact on a study when those who consent to participate in research differ from those who do not or cannot consent.**

It leads to **poorer patient care**, as evidence may be **unreliable or invalid** (low response rate), **misleading** (failure to capture an important association )

C Junghans et al., Heart **2007**; 93:1024 (London)

M King et al., JAMA **2005**; 293:1089 (London, Manchester)

# CHECKLIST TO LOOK FOR EFFECTS OF CONSENT BIAS

- a. **Are the total numbers in the study approached for consent reported?** If not, it is difficult to gauge how representative this paper is of the patient population.
- b. **Is the percentage response/consent rate reported?** A response rate of **at least 60%** is common. A low response rate may lead to diminished validity for the patient population.
- c. **Is the consent method documented?**
  - Is it opt-in or active consent (more likely to lead to bias).
  - or opt-out or passive consent (less likely to lead to bias).
- d. **Do the authors report the impact of their approach on generalisability or validity on their study?**
- e. **Are the baseline characteristics of the patients in the study broadly similar to the patient population?**

C Junghans et al., Heart **2007**; 93:1024 (London)

M King et al., JAMA **2005**; 293:1089 (London, Manchester)

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## Double-Blind / Open Label, Non Inferiority, Stop,

Double-blindness is one of the fundamental principles of avoiding biases. The underlying issue is that study participants and investigators have preconceived notions. Manufacturers of new interventions, in addition, have a commercial stake in the trial outcome. **Conducting double-blind trials introduces many challenges in terms of both effort and costs.** The alternative— open trial designs— may be much costlier to society if the trial findings are biased.

## Double-Blind / Open Label, Non Inferiority, Stop,

There is a common belief that data generated by **double-blind studies are the least subject to bias**. It has been estimated that the **absence of double-blinding exaggerates treatment effects by 14%**.

**Opponents, usually argue that it creates an artificial environment that does not reflect true clinical practice:** tends to select certain patients, patients are less willing to participate, are effort- and time-consuming studies, and physicians have **a selection bias in including lower-risk patients**.

M Casteels, B Flamion. J Thr Haem **2007**; 6:232 (Leuven)

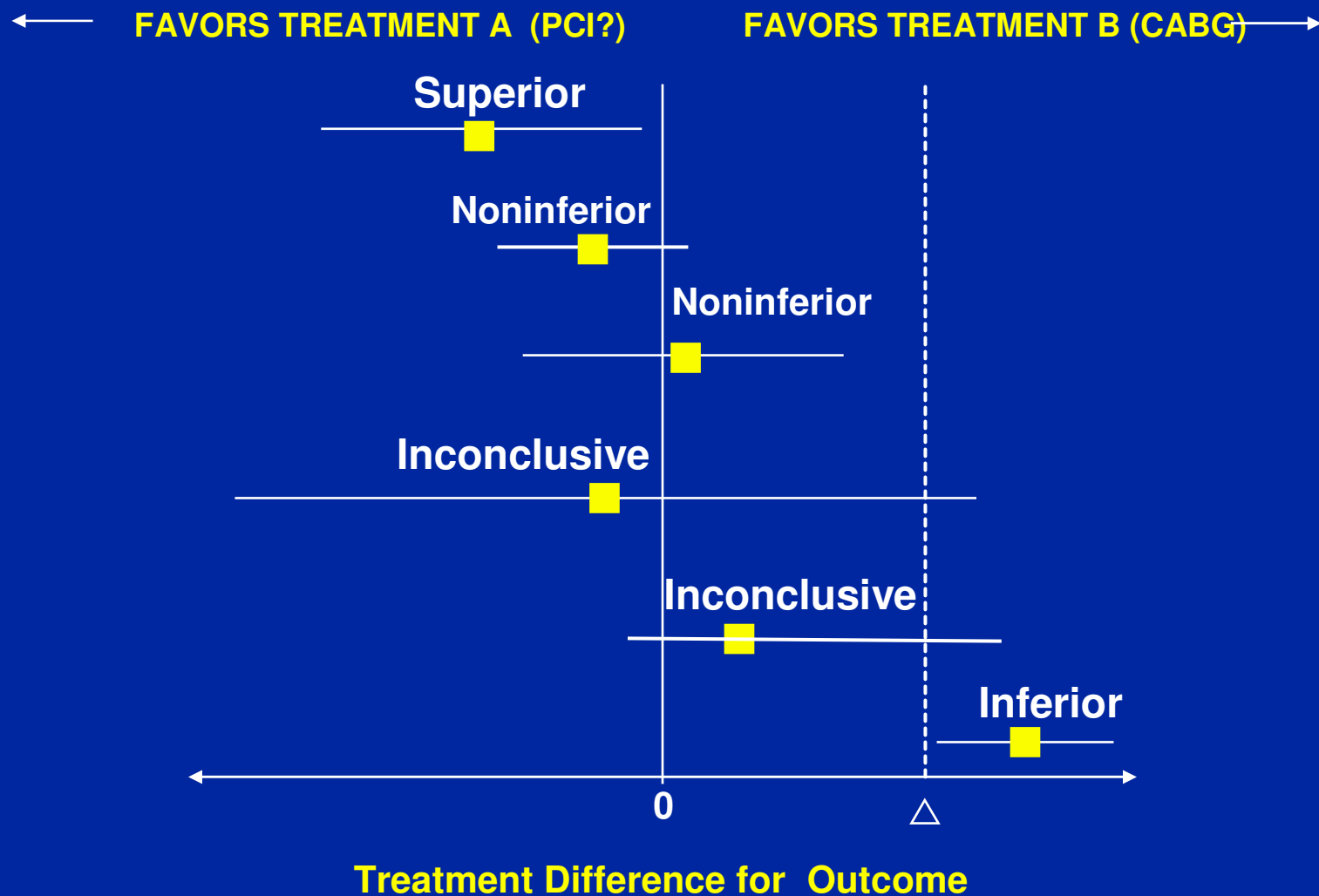
## **Double-Blind / Open Label, Non Inferiority, Stop,**

**If blinding is not possible, adjudication of endpoint events by an independent committee, blinded to the treatment of the patient, is important.** This has become known as the **PROBE** (Prospective, Open, Blinded Endpoint design). PROBE trials might be cheaper and simpler than double-blind one, but are **less precise.**

**A package comprising both PROBE and double-blind pivotal randomized trials, with internal consistency, offers the highest level of information as a basis for marketing authorization.**

**M Casteels, B Flamion. J Thr Haem 2007; 6:232 (Leuven)**

# Double-Blind / Open Label, Non Inferiority, Stop,



Modified from G Piaggio et al. JAMA 2006; 295:1152

## **Double-Blind / Open Label, Non Inferiority, Stop,**

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**Noninferiority and equivalence trials aim to show that the experimental treatment is not clinically worse (noninferior) or clinically similar (equivalent) to a control treatment.** MEDLINE and the Cochrane Central Registry of Controlled Trials were analyzed from Jan 2003 and Dec 2004. A total of **162 reports** were included. **The margin** was defined in **96.3%**, with its **justification** in only **20.4%**. About **21.6%** did not describe **a sample size** and an additional **6.8%** did not take into account a **prespecified noninferiority**. **Only 20.3%** fulfilled reporting requirements, **12.1%** with misleading conclusions.

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A Le Henanff et al., JAMA **2006**; 295:1147 (Tours)

## Double-Blind / Open Label, Non Inferiority, Stop,

**The CONSORT** (Consolidated Standards of Reporting Trials) Statement including was developed to help authors improve their reporting of randomized controlled trials. **Its primary focus was on individually randomized trials with 2 parallel groups that assess the possible superiority of one treatment compared with another** but is now being extended to other trial designs. **The intent is to improve reporting of noninferiority and equivalence trials,** enabling readers to assess their results and conclusions.

**CONSORT** (G Piaggio et al.) JAMA **2006**; 295:1152

## **Double-Blind / Open Label, Non Inferiority, Stop,**

**Of 143 RCTs stopped early for benefit, the majority or 92 were published in 5 high-impact medical journals.**

**Typically, these were industry-funded drug trials. About 94% of the 143 RCTs did not report at least 1 of the required parameters.**

**Trials with fewer events yielded greater treatment effects (odds ratio, 28; 95% CI, 11-73). Becoming more common, often fail to report relevant information about the decision to stop early, and show implausibly large treatment effects, particularly when the number of events is small. Such trials should be viewed with skepticism.**

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## **- Statistical Methodology**

Double-Blind, Open Label, Non Inferiority, Early Stop,

Subgroups, Observational / Registry, Surrogate End-Points,

## **-Trials or EBM vs the Individual Patient**

# Subgroups, Observation / Registry, Surrogates

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## In the Abstract:

Present subgroup results only if the subgroup analyses were based on a **primary study outcome**.

## In the Methods section:

Indicate the **number of prespecified subgroup analyses that were performed** and the number of prespecified subgroup analyses that are **reported**.

## In the Results section:

When possible, base analyses of the heterogeneity of treatment effects on **tests for interaction**, and present them along with effect estimates within each level of each baseline covariate analyzed.

## In the Discussion section:

**Avoid overinterpretation** of subgroup differences, and provide supporting or **contradictory data from other studies**, if any.

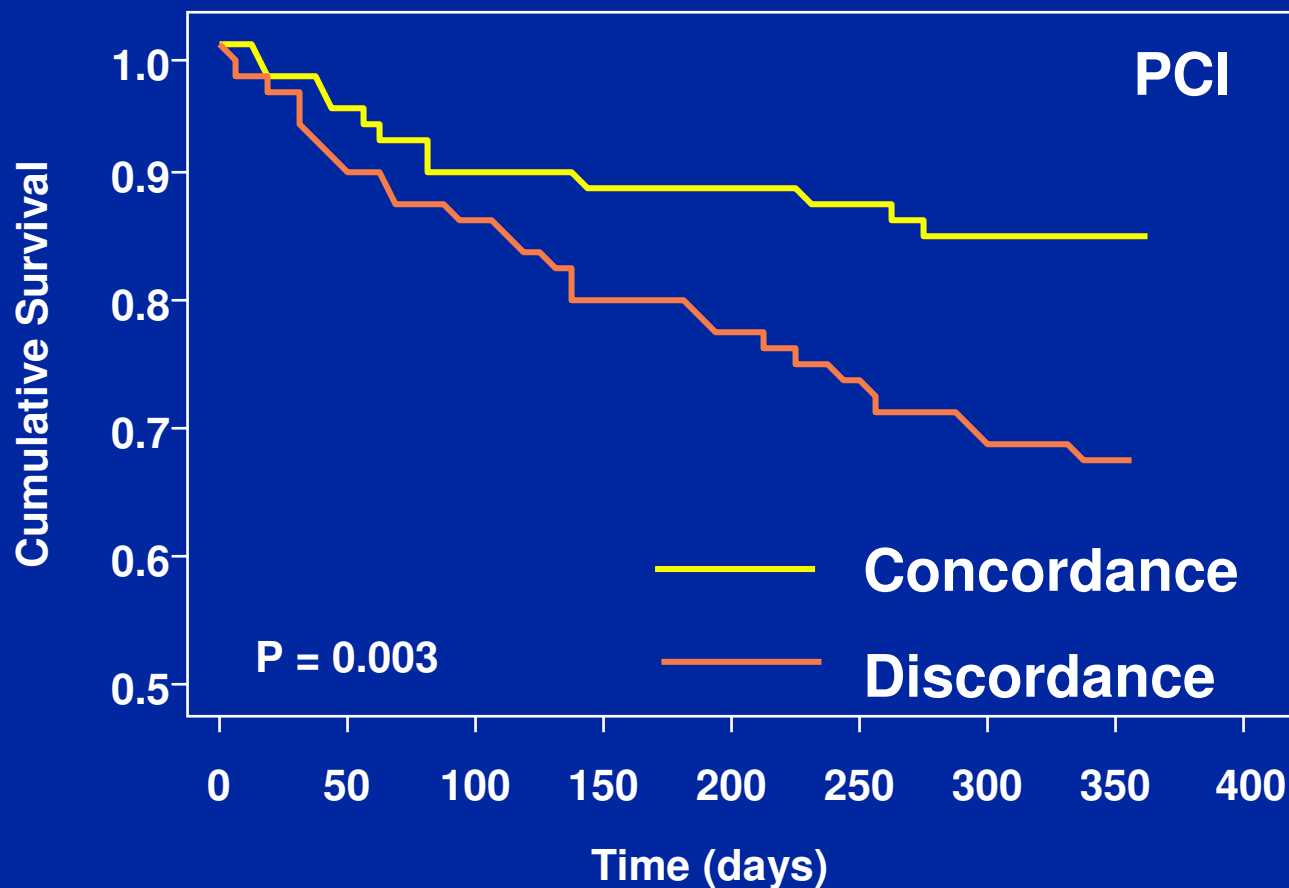
## Subgroups, Observation / Registry, Surrogates

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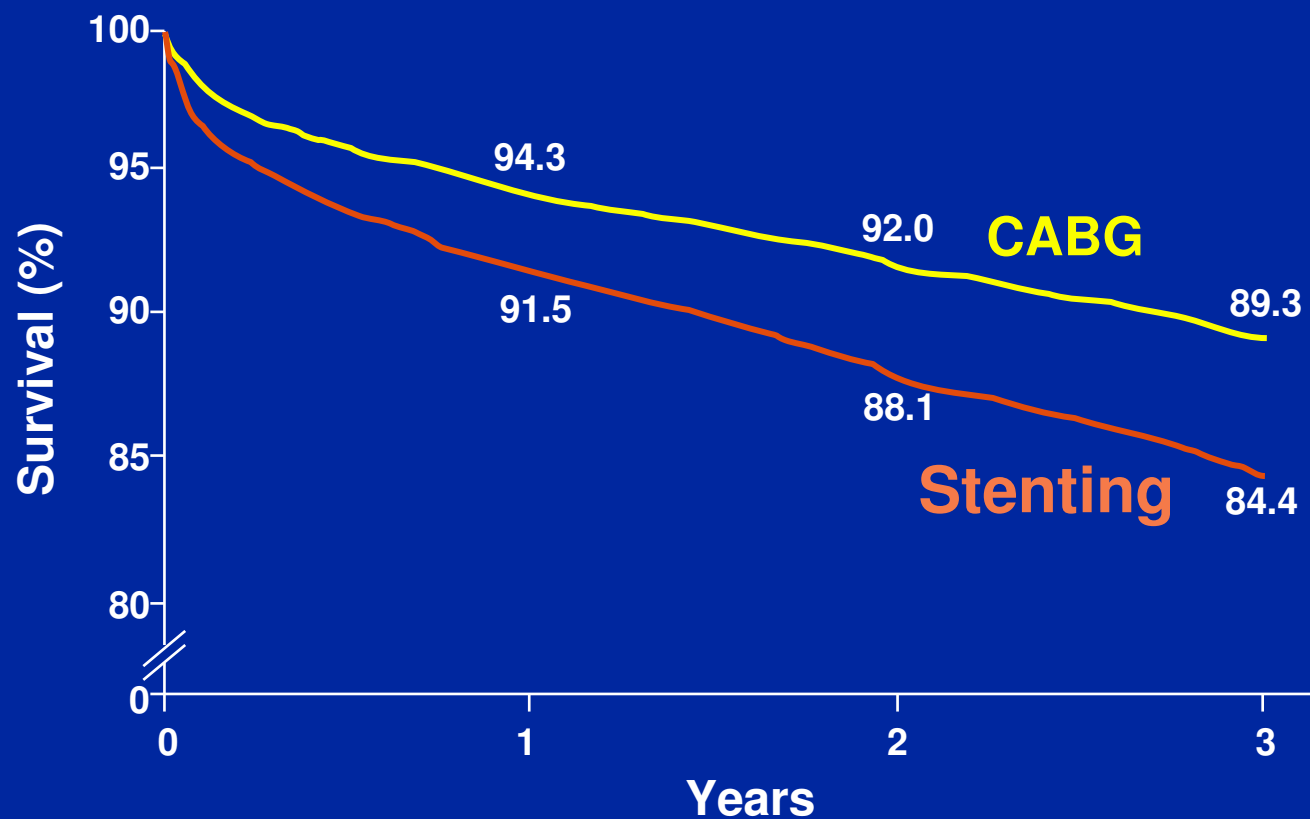
**Much biomedical research is observational.** The reporting of such research is often **inadequate**, which hampers the assessment of its strengths and weaknesses and of a study's **generalizability**. **The Strengthening the Reporting of Observational Studies in Epidemiology –STROBE-** initiative developed recommendations in a checklist of **22 items** on what should be included in an accurate and complete report of an observational study.

STROBE (E von Elm et al.) Lancet **2007**; 370:1453

# 1) CONCORDANCE OF TREATMENT ASSIGNMENT ALTERS OBSERVED BENEFIT ONLY FOR PATIENTS RANDOMIZED TO PCI



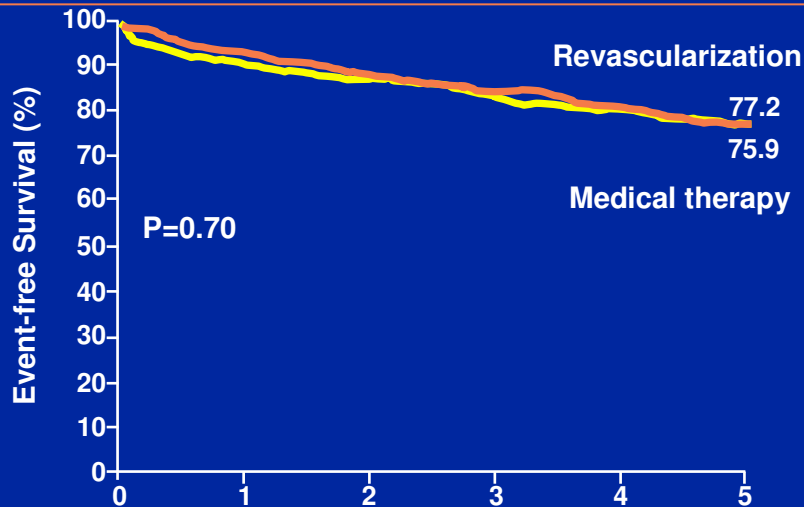
**2) ADJUSTED SURVIVAL AMONG PATIENTS WITH 3VD (PROX. LAD)  
(PART OF NY REGISTRY 1997-2000 – STENT 22102 – CABG 37212)**



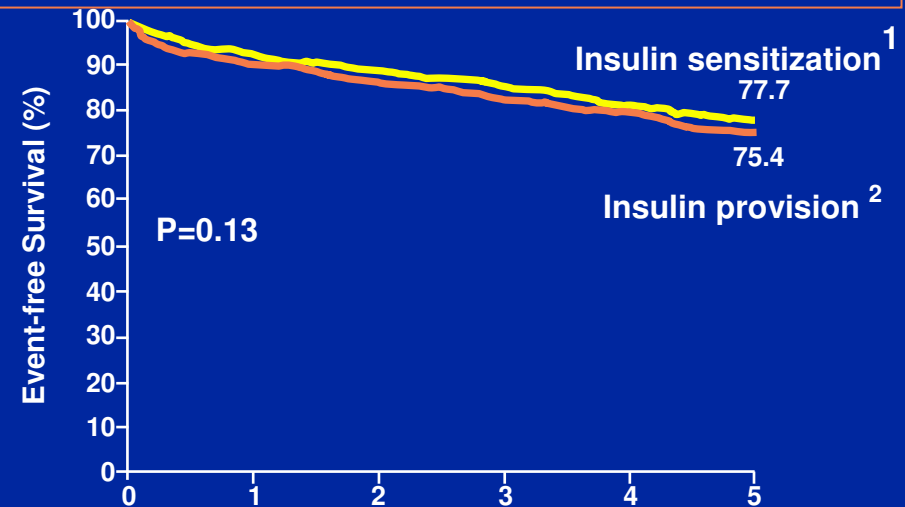
**NY State (El Hanna et al.) NEJM 2005; 352**

### 3) BARI 2D – TYPE 2 DIABETES AND STABLE IHD

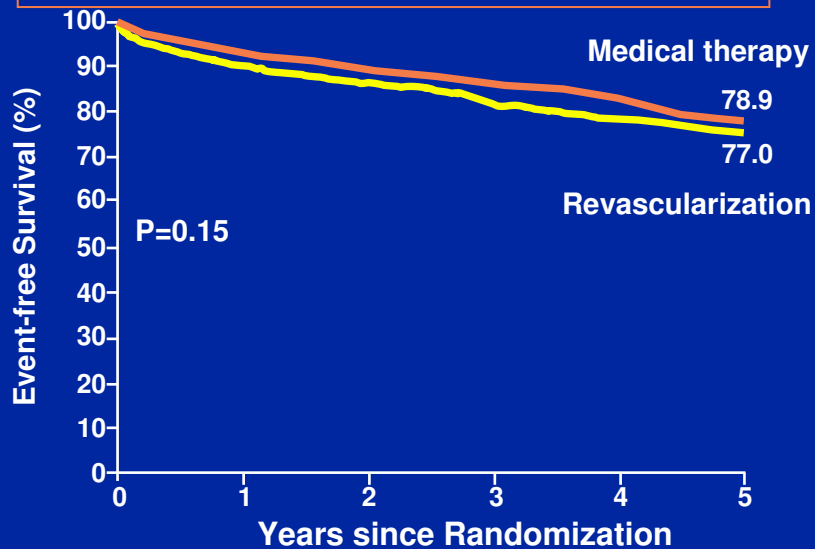
Freedom from Major CV Events, Revascularization vs. Medical Therapy



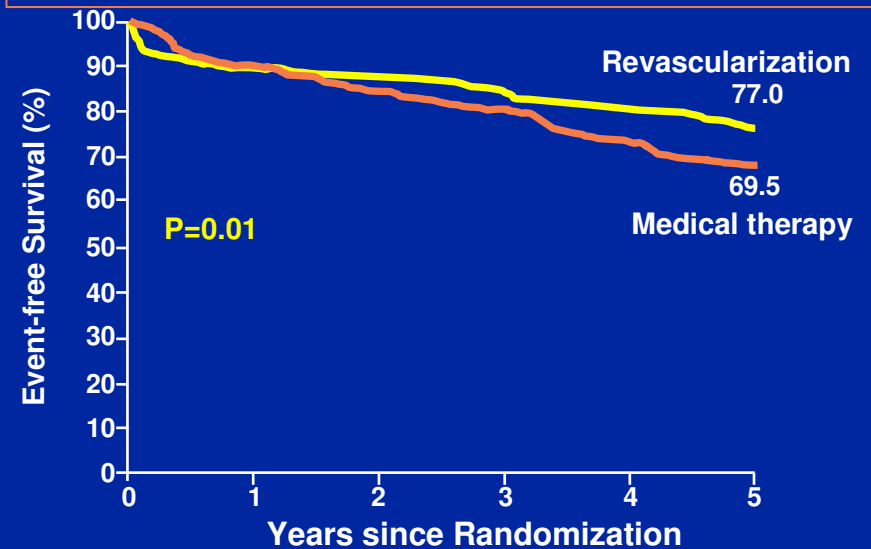
Freedom from Major CV Events, Insulin Sensitization vs. Insulin Provision



Freedom from Major CV Events in PCI Stratum



Freedom from Major CV Events – MI - in CABG Stratum



## Subgroups, Observation / Registry, Surrogates

Therapeutic development is expensive, inefficient, and is generally focused on short-term treatment effects. **Could measures of disease progression, combined with trends on clinical outcomes and post-marketing surveillance to assess safety, serve as the foundation for therapeutic development? Experience and principles of clinical research tell us no. Improved reliability and capacity require:** more efficient trial methods, streamlined regulatory processes, rational privacy protection, electronic medical records and recruitment of a larger proportion of the clinical community in clinical trials.

CB Granger et al., J Am Coll Cardiol **2006**; 48:434 (Duke)

*“CLINICAL TRIALS, DO THEY ADDRESS THE REAL WORLD OR MY PATIENT ?”*  
*“CLINICAL TRIALS (EFFICACY) AND THE REAL WORLD (EFFECTIVENESS)”*

## **-Introductory Background**

Definition - EBM, Phases, Progress, Megatrials

## **- Exclusion / Inclusion - Bias**

Industry, Journals, Low Recruitment

Sex, Elderly, Race, Developing Countries

## **-Registration**

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## **-Trials or EBM vs the Individual Patient**

# 1) *POTENTIAL REASONS FOR DIFFERENCES BETWEEN THE EFFICACY (TRIALS) AND EFFECTIVENESS (REAL WORLD)*

## Study design

**Trial protocol forces uncommon clinical scenarios**

Comparison group does not represent current standard of care

Outcomes include less meaningful end points

## Patient selection and Biases

**Biases** in the patients who are **eligible** for a therapy

**Biases** in patients who are **ultimately selected** for (or agree to) a therapy

## Therapeutic implementation

**Complex and multifaceted therapies** are challenging to implement

Procedural experience of providers influences outcomes

## Environment of the healthcare delivery system

**Limited availability of providers or resources**

**Inadequate levels of reimbursement**

## 2) Trials or EBM vs the Individual Patient Integrating Patient Preferences – The next Step

Modern medicine is dominated by 2 paradigms, EBM and patient-centered medicine. The trend toward patient-centered medicine is characterized by an **increased emphasis on patient experience rather than the patient's disease, and an increased role for patients in decision making.** Clinical practice guidelines are becoming more widely used as a method for standardizing clinical practice and building pay-for-performance programs. **By not getting guidelines right for patients, perverse incentives may be introduced for clinicians to advocate treatments that are counter to what patients want & value.**

M Krahn et al., JAMA 2008; 300:437

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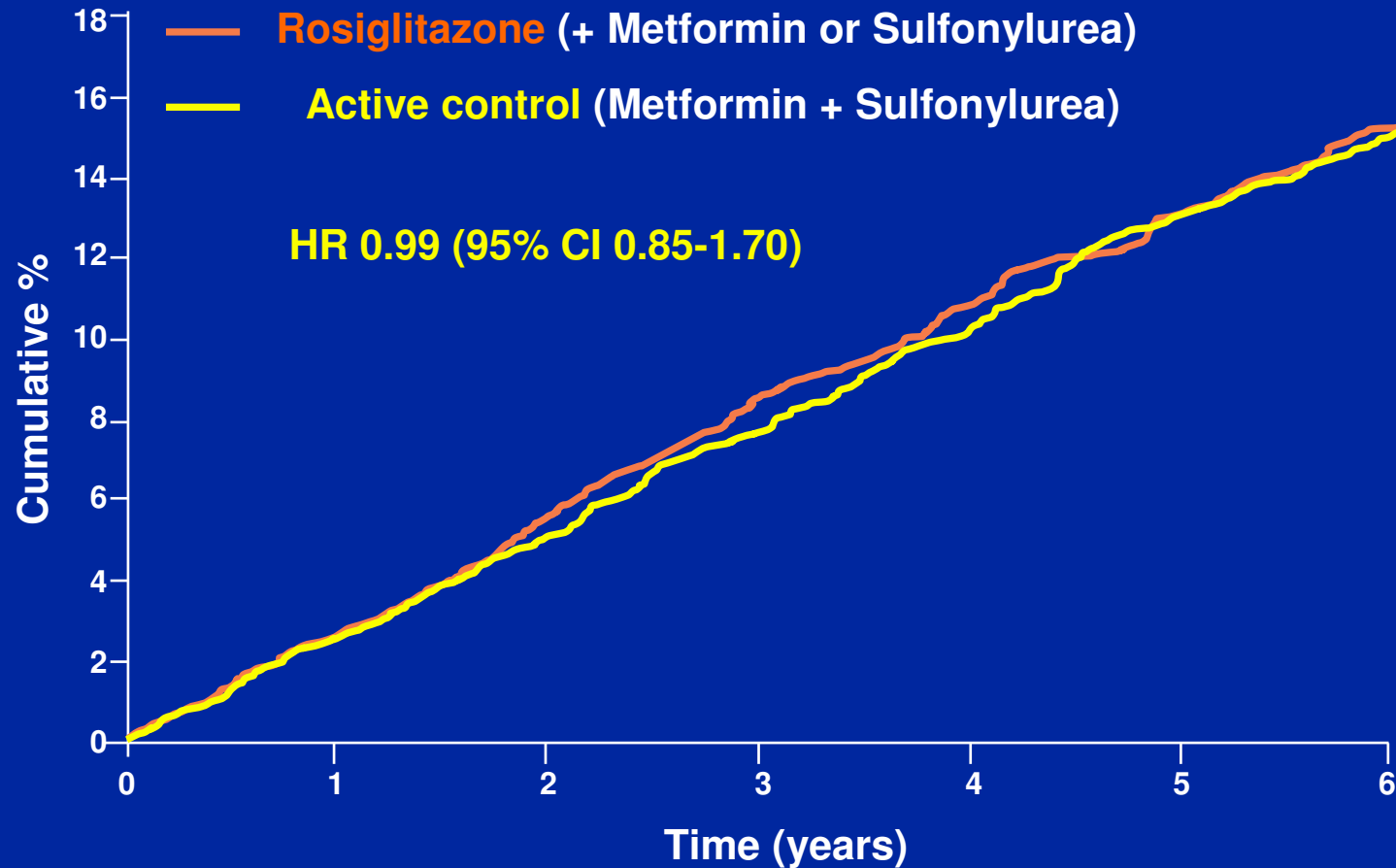
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# ROSIGLITAZONE – TIME TO THE PRIMARY ENDPOINT: CV DEATH OR CV HOSPITALIZATION (N=4447)



Heart Failure – HR 2.1

**RECORD** (PD Home et al.) Lancet; **June 5, 2009**

# Effect of Ramipril and of Rosiglitazone on Carotid Intima-Media Thickness in People With Impaired Glucose Tolerance or Impaired Fasting Glucose

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The aim of this study was to evaluate effects of the angiotensin-converting enzyme (ACE) inhibitor ramipril and the thiazolidinedione (TZD) rosiglitazone on carotid intima-media thickness (CIMT) in people with impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG). **In people with IGT and/or IFG without cardiovascular disease and diabetes, treatment with ramipril had a neutral effect on CIMT, whereas rosiglitazone modestly reduced CIMT progression.**

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**STARR** (EM Lonn et al.) JACC 2009; 53:2028