Evidence Based Medicine: Evaluating the Literature for Optimal Clinical Decisions

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Objectives

- Identify potential sources of commercial bias in publications
- List the most reliable sources of unbiased medical information
- State the value of disclosure, trial registration, and peer review
- Critically analyze a study for intrinsic & extrinsic validity

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Disclaimers

- I have no financial conflicts of interest. (no stock, honoraria, consultant services, speakers board etc.) I do occasionally eat at a sponsored CE program
- For this presentation I'm getting paid attention (I hope…)
- Employed by The Regional Medical Center at Memphis and the University of Tennessee College of Pharmacy

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There is so much information! And lots of it is garbage!

- Patients & Colleagues are counting on us to stay current and accurate to make best decisions
- You need a strategy!
  - Getting information:
    - Journal Clubs (survey vs. detailed analysis)
    - Emailed TOC, RSS (Really simple syndication), Podcasts,
    - Storing Information
    - PDF's (paperless)
  - Analyzing information
    - This session

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Your Desk?

5

Types of articles

- **Reviews (+/- case reports)**
  - **Vary by source**
  - New England Journal of Medicine
  - Lancet, JAMA etc.
  - Medical Letter Treatment Guidelines
  - vs.
    - Journal of irreproducible results…

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Types of articles (2)

- **Guidelines**
  - Published by a (hopefully) authoritative organization
  - Index at: www.guidelines.gov
  - My favorite sources:
    - Cardiology: www.americanheart.org
    - Diabetes: www.diabetesjournals.org
    - Infectious Diseases: www.cdc.gov & www.idsociety.org

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Types of Studies

- Cost – Effectiveness analysis (yuck)
  - $ per year of life saved…
- Meta-Analysis
  - Pool results from "similar" studies
  - Try to increase number of patients (power) to detect differences not seen in small individual studies

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Types of Studies (2)

Observational

- Cohort = Retrospective or Prospective
  - Patients with exposure / risk & comparator followed for development of disease
- Case – Control = Retrospective
  - Patients with disease vs similar pts without
    - Look back for exposures / risks
    - Good for rare diseases / events
    - Hypothesis generating

Interventional

- Randomized Controlled Trials (RTC's)
  - Gold standard – test a hypothesis prospectively

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Publication Bias

- "Innocent"
  - Positive results tend to get published vs trials showing no benefit
- "Dubious"
  - Strings attached (company does data analysis)
  - Ghost writing
  - Supplements & Symposium
  - "Guidelines" by company sponsored groups
  - Phase 4 trials

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Publication Bias (2)

- Published company sponsored studies 4 x as likely to favor company's drug
  BMJ 2003;326:1167, JAMA 2003;289:454-465.
- Not a new problem
  - Bioequivalence of levothyroxine - 1996
    - Company sponsored, done at UCLA, found generic equivalent, pulled by company from JAMA after at printer.
      JAMA 1997;277:1205-1213, 1238-1243

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Publication Bias (3)

- GSK suppressed unpublished data of two negative trials of paroxetine in children
- Meta-analysis of SSRIs in children that included published & unpublished data found risks could outweigh benefits. (excluded fluoxetine)
  - Opposite of findings using published data
    Lancet 2004; 363:1341-45
- New York attorney general sues GSK

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Publication Bias (4)

Dangerous Deception — Hiding the Evidence of Adverse Drug Effects

Jerry Avorn, M.D.

September 30 is becoming a day of infamy for drug safety. On that date in 2004, Merck announced that rofecoxib (Vioxx) doubled the risk of myocardial infarction and stroke, and the company

Observational Studies of Drug Safety — Aprotinin and the Absence of Transparency

William R. Hiatt, M.D.

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Of course you can just make up data…

Publication Bias (5)

- Alabama physician Maria Anne Kirkman-Campbell was charged on Aug. 29, 2003, with falsifying clinical trial data in study 3014, a randomized, open-label comparative study.
- She pleaded guilty to one count of mail fraud and was sentenced on March 25, 2004, to 57 months in federal prison and was fined $557,251. She was also ordered to pay restitution of $925,774 to Sanofi-Aventis.
- More than 24,000 subjects were enrolled in study 3014, according to FDA documents, and treated with either telithromycin or amoxicillin-clavulanic acid.
- Kirkman-Campbell had enrolled the most patients into the study.

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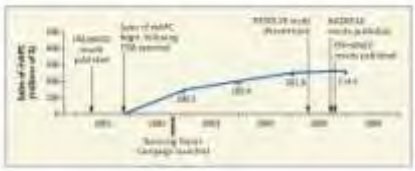
Surviving Sepsis — Practice Guidelines, Marketing Campaigns, and Eli Lilly

Timeline of Controlled Trials of rhAPC, Regulatory Actions, Yearly Sales, and the Marketing Initiative by Eli Lilly



Eichacker P et al. N Engl J Med 2006;355:1640-1642

The NEW ENGLAND JOURNAL of MEDICINE

Ways to avoid bias

- Disclosure
  - Clearly identify conflicts of interest
    - Real vs. perceived
- Trial Registration
  - Minimize suppression of negative results
- Peer Review
  - Gold standard
  - Best if blinded and peers are experts

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Disclosure of Conflict of Interests

- Guidelines recently overhauled
  - 2002 AMA, ACP, AC-CME
  - 2002 PhRMA
  - 2003 OIG of DHHS
- Why?
  - "troubling influence that pharmaceutical marketing can have on patient care"
  - Medicare prescription-drug benefit cost concerns
  - Accumulated Federal "fraud and abuse" law
  - NEJM 2004;351:1891-1900

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Disclosure of Conflict of Interests (2)

Health Industry Practices That Create Conflicts of Interest

A Policy Proposal for Academic Medical Centers

Troyen A. Brennan, MD, MPH
David J. Rothman, PhD
Linda Blank
David Blumenthal, MD, MPP
Susan C. Chimonas, PhD
Jordan J. Cohen, MD
Janlori Goldman, JD
Jerome P. Kassirer, MD
Harry Kimball, MD
James Naughton, MD
Neil Smelser, PhD

THE CURRENT INFLUENCE OF market incentives in the United States is posing extraordinary challenges to the principles of medical professionalism. Physicians'

Conflicts of interest between physicians' commitment to patient care and the desire of pharmaceutical companies and their representatives to sell their products pose challenges to the principles of medical professionalism. These conflicts occur when physicians have motives or are in situations for which reasonable observers could conclude that the moral requirements of the physician's roles are or will be compromised. Although physician groups, the manufacturers, and the federal government have instituted self-regulation of marketing, research in the psychology and social science of gift receipt and giving indicates that current controls will not satisfactorily protect the interests of patients. More stringent regulation is necessary, including the elimination or modification of common practices related to small gifts, pharmaceutical samples, continuing medical education, funds for physician travel, speakers bureaus, ghostwriting, and consulting and research contracts. We propose a policy under which academic medical centers would take the lead in eliminating the conflicts of interest that still characterize the relationship between physicians and the health care industry.

JAMA. 2006;295:429-433 www.jama.com

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Disclosure of Conflict of Interests (3)

- Gifts (including meals) - none
- Samples – vouchers only
- Formularies – exclude conflicted members
- CME – exclude all direct & indirect support (give to central repository)
- Travel – give to central repository
- Speakers Bureaus/Ghostwriting by faculty – none
- Consulting & Research – only under explicit contracts

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Clinical Trial Registration

- Cannot practice evidence-based medicine if you don't have all the evidence.
- Trial Registration 1st proposed in the 1970's
- www.ClinicalTrials.gov (12,000 trials to date)
  - Serious / life-threatening conditions
  - Not mandatory
    - Registration of applicable cancer trials:
      - 91% government sponsored studies
      - 49% industry-sponsored trials
- PhRMA's: www.clinicalstudyresults.org

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Clinical Trial Registration (2)

- Joint statement by ICMJE
  - "require, as a condition of publication, registration in a public trials registry. Trials must register at or before the onset of patient enrollment."
    NEJM 2004;351:315-7
  - International Committee of Medical Journal Editors. JAMA, NEJM, NZMJ, NMJ, CMAJ, Lancet, Medline, AnIMed, CMJ, DJM, JDMA, MJA

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So who can you trust?

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My favorite sources

- General drug information
  - AHFS, Micromedex, Facts & Comparisons
  - IV compatibility: Trissles, Kings…
  - PDA: Epocrates, Lexicomp
  - ID: Sanford Guide
  - I DON'T like "Up To Date"

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My favorite sources (2)

- Keeping up
  - Medical Letter (www.medicalletter.org)
    - $89 / year
  - Medical Letter Treatment Guidelines
    - $98 / year
  - Pharmacist Letter (www.pharmacistletter.org)
    - $85 / year
  - Ignorance is cheap…

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My favorite sources (3)

- Journals
  - ***New England Journal of Medicine***
    The best medical journal ($149 / year)
    - JAMA, Lancet, Annals/Archives
  - Medial Subspecialty
    - ID: Idsociety.org; CDC.gov et al

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EBM
Evidence Based Medicine

BMJ 1996;312:71-72

- Evidence based medicine is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients.
- The practice of evidence based medicine means integrating individual clinical expertise with the best available external clinical evidence from systematic research.

Vs Experience or Eloquence Based

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Studying a study

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Testing a Test (Biostats)

- Pharmacist's Letter Detail Document #210610 2005;21:1-26.
- Annals of Emergency Medicine series 1997
- Altman DG "Why we need confidence intervals" World J Surg 2005;29:554-556
- Wen L et al "Number needed to treat: A descriptor for weighing therapeutic options" Am J Health-Sys Pharm 2005;62:2031-2036

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So you have a study to read

- Ask yourself – how much do I care?
  - Reflects your clinical practice and patients
  - Determines how much detail to get in to
    - Title, abstract or whole thing
    - If you are going to quote it, you've got to read it (the whole thing), otherwise abstract may do
      - frequently violated by physicians
  - Some articles must be read just to keep the drug reps honest…

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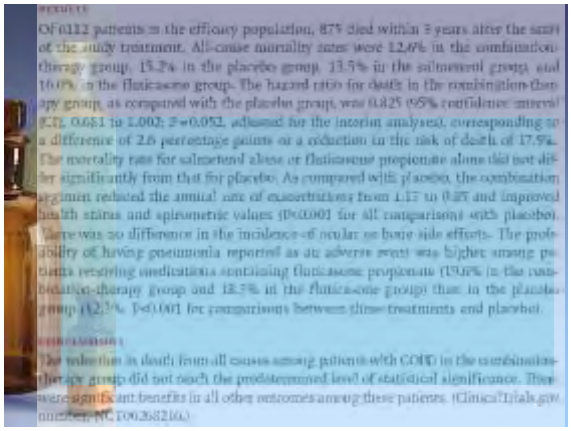
The Structure of a Study

- Front:
  - Title, Authors, Affiliations, NCT #
  - Abstract
    - Background, Methods, Results, Conclusions
- Middle:
  - Intro, Methods, Results, Discussion
- Back:
  - Disclosures & References
- Editorials & Letters

Abstract (1)

- Patients: COPD
- Regimens:
  - Salmeterol 50 mcg + Fluticasone 500 mcg
  - Salmeterol
  - Fluticasone
  - Placebo
- Duration : 3 years
- Primary Outcome:
  - Death (Combo vs Placebo)
  - 2nd: Exacerbations, health status, spirometry



Abstract (2)

- Mortality:
  - 12.6% Combo vs 15.2% Placebo
    - HR 0.825 (95% CI 0.861 – 1.002; P = 0.052)
    - Absolute reduction = 2.6% (15.2 – 12.6)
    - Reduction of 17.5%
    - Salmeterol = Fluticasone = Placebo
- Other Outcomes (Combo vs Placebo)
  - Significantly reduced exacerbation frequency (0.85 vs 1.13 per year), improved health status & spirometric values (p < 0.001)
  - Significantly more pneumonia with fluticasone (19.6% with combo, 18.3% fluticasone alone) vs placebo (12.3%, P < 0.001).
- Conclusions
  - Mortality didn't reach predetermined level of Stat Significant

Must Consider

- Intrinsic vs Extrinsic Validity
  - Intrinsic:
    - Did the study really prove what it set out to and reported to prove (was it a "good" study)
  - Extrinsic:
    - Which "real-world" patient population can this result be appropriately applied to and how will it change my practice (if at all)

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Intrinsic Validity

- Hypothesis
- Funding, Registration, IRB
- Patient Enrolment
- Randomized
- Blinded
- Controlled
- Treatment group = control group
  - At beginning of study
  - During the study (except for the intervention)

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Intrinsic Validity (2)

- All patients accounted for
  - How many dropped out & why
- Analyzed as randomized
  - Intent-to-treat vs. on protocol
- Outcome measures pre-defined & meaningful
  - Primary vs secondary; composite
  - Mortality vs. surrogate markers or scales

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Intrinsic Validity (3)

- What are the differences between treatment arms
- Are the results statistically significant
  - Confidence intervals & P - values
- Are the results clinically significant
- What is the magnitude of the benefit
  - Absolute & Relative Risk Reduction
  - Number Needed to Treat or Harm

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Basic Biostats

	Disease Positive	Disease Negative
Result Positive	A True Positive (Sensitive)	B False Positive Type I Error Alpha = 0.05
Result Negative	C False Negative Type II Error Beta = 0.8	D True Negative (Specific)

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Basic Biostats (2)

- Type I error = False Positive
  - Find something that isn't there
  - P values $\leq$ 0.05
    - accept a 5% chance of false positive result
- Type II error = False Negative
  - Miss something that is there
  - Power = (1- Beta level)
  - More patients = better chance of finding small differences

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Basic Biostats (3)

- Sensitivity
  - Screen / find those with disease
  - TP/(TP + FN)
- Specificity
  - Confirm diseases presence
  - TN/(TN + FP)

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Basic Biostats (4)

- Statistically Significant (P < = 0.5)
  - There is a less 5% probability that the difference observed was due to chance
  - Yes or no answer, not magnitude
- Confidence Intervals (usually 95% CI)
  - Most useful for odds-rations & relative risks, gives idea of magnitude of difference
  - If it less than 1 then it is NOT stat-sig

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Basic Biostats (5)

- **Relative Risk (RR)**
  Pt = A/(A+B)
  Pc = C/(C+D)
  Event prob Tx
  Event prob Cnt
- **Odds Ratio (OR)**
  Pt x(1-Pc)
  Pc x(1-Pt)

	Dz +	Dz -
RF + Or Tx	**A** Dz + RF +	**B** Dz – RF +
RF – Or Cnt	**C** Dz + RF -	**D** Dz – RF -

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Basic Biostats (5)

- **Absolute Risk Reduction (ARR)**
  (C/C+D) - (A/(A+B)
  event prob Cnt (Pc)
  – event prob Tx (Pt)
- **Number Needed to Treat (NNT)**
  = 1 / ARR

	Dz +	Dz -
RF + Or Tx	**A** Dz + RF +	**B** Dz – RF +
RF – Or Cnt	**C** Dz + RF -	**D** Dz – RF -

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Extrinsic Validity

- Are these patients similar to mine
  - Demographics, co-morbidities, severity
  - Monitoring, access to healthcare, compliance
- Are these outcomes meaningful to my patients
- Are the results worth the risks & costs vs. other therapies (NNT, NNH?)
- Should / can I change practices to match

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Common abuses of literature

- Confusing Statistical and Clinical Significance
- Pooling Groups / Composite Outcomes
  - CAPRIE: atherosclerotic vascular disease
    - ischemic stroke, recent myocardial infarction, or symptomatic peripheral arterial disease
- Retrospective & Subset Analysis
  - Generate hypothesis, not prove them!
  - Wunderink et al Linezolid vs Vanco for MRSA VAP *Chest.* 2003;124:1789-1797.
- Discussing and concluding to much
  - Drug reps and inferior journals

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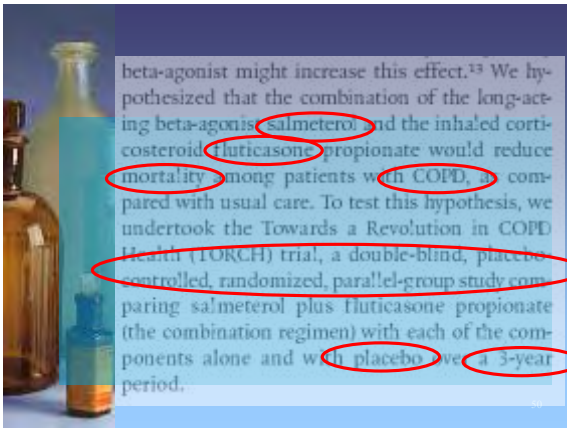
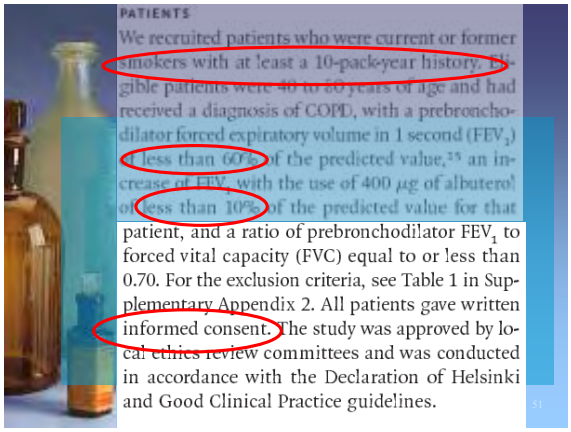
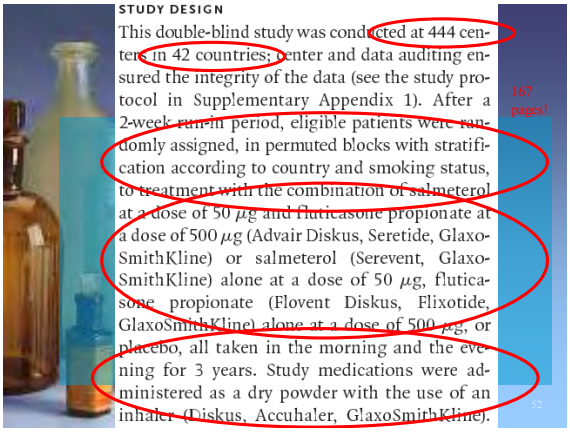

beta-agonist might increase this effect.[13] We hypothesized that the combination of the long-acting beta-agonist salmeterol and the inhaled corticosteroid fluticasone propionate would reduce mortality among patients with COPD, as compared with usual care. To test this hypothesis, we undertook the Towards a Revolution in COPD Health (TORCH) trial, a double-blind, placebo-controlled, randomized, parallel-group study comparing salmeterol plus fluticasone propionate (the combination regimen) with each of the components alone and with placebo over a 3-year period.

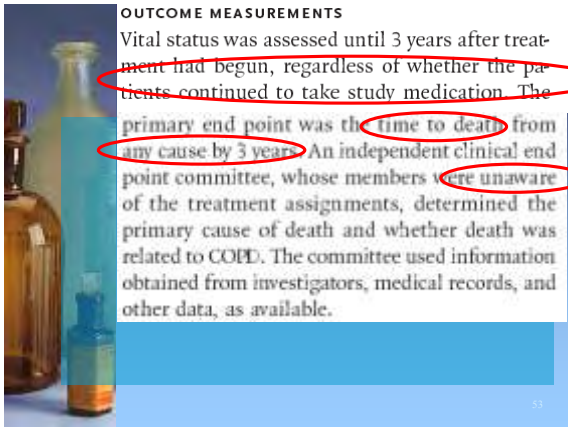

PATIENTS

We recruited patients who were current or former smokers with at least a 10-pack-year history. Eligible patients were 40 to 65 years of age and had received a diagnosis of COPD, with a prebronchodilator forced expiratory volume in 1 second (FEV_1) of less than 60% of the predicted value,[15] an increase of FEV, with the use of 400 μg of albuterol of less than 10% of the predicted value for that patient, and a ratio of prebronchodilator FEV_1 to forced vital capacity (FVC) equal to or less than 0.70. For the exclusion criteria, see Table 1 in Supplementary Appendix 2. All patients gave written informed consent. The study was approved by local ethics review committees and was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

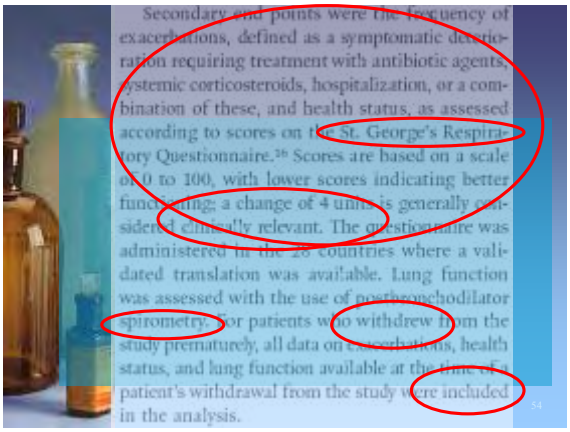

STUDY DESIGN

This double-blind study was conducted at 444 centers in 42 countries; center and data auditing ensured the integrity of the data (see the study protocol in Supplementary Appendix 1). After a 2-week run-in period, eligible patients were randomly assigned, in permuted blocks with stratification according to country and smoking status, to treatment with the combination of salmeterol at a dose of 50 μg and fluticasone propionate at a dose of 500 μg (Advair Diskus, Seretide, GlaxoSmithKline) or salmeterol (Serevent, GlaxoSmithKline) alone at a dose of 50 μg, fluticasone propionate (Flovent Diskus, Flixotide, GlaxoSmithKline) alone at a dose of 500 μg, or placebo, all taken in the morning and the evening for 3 years. Study medications were administered as a dry powder with the use of an inhaler (Diskus, Accuhaler, GlaxoSmithKline).

167 pages!


OUTCOME MEASUREMENTS

Vital status was assessed until 3 years after treatment had begun, regardless of whether the patients continued to take study medication. The primary end point was the time to death from any cause by 3 years. An independent clinical end point committee, whose members were unaware of the treatment assignments, determined the primary cause of death and whether death was related to COPD. The committee used information obtained from investigators, medical records, and other data, as available.


Secondary end points were the frequency of exacerbations, defined as a symptomatic deterioration requiring treatment with antibiotic agents, systemic corticosteroids, hospitalization, or a combination of these, and health status, as assessed according to scores on the St. George's Respiratory Questionnaire.[16] Scores are based on a scale of 0 to 100, with lower scores indicating better functioning; a change of 4 units is generally considered clinically relevant. The questionnaire was administered in the 25 countries where a validated translation was available. Lung function was assessed with the use of postbronchodilator spirometry. For patients who withdrew from the study prematurely, all data on exacerbations, health status, and lung function available at the time of a patient's withdrawal from the study were included in the analysis.

SAFETY EVALUATION

Adverse events and medications were reviewed at each study visit. Additional information was collected about any fractures, classified as either traumatic or nontraumatic, with nontraumatic fractures considered to be caused by falls from less than standing height or falls occurring spontaneously. Dual-energy x-ray absorptiometry at the hip and lumbar spine and slit-lamp examinations were performed on patients' entry into the study and annually thereafter in a safety substudy conducted in the United States and involving 658 patients.

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STATISTICAL ANALYSIS

All reported data analyses were prespecified. Assuming a 17% mortality rate in the placebo group at 3 years,[17] we estimate that 1510 patients would be needed for each study group to detect a reduction in mortality of 4.3 percentage points in the combination-therapy group, as compared with the placebo group (hazard ratio for death, 0.728), in a two-sided alpha level of 0.05 with 90% power. Two interim analyses of death from any cause were planned to assess whether there was overwhelming evidence of a benefit from the combination regimen, as compared with placebo, or of harm in any study group; these analyses were performed by the independent safety and efficacy data monitoring committee according to the method of Whitehead.[18] As a consequence, the P value for the primary comparison between the combination regimen and placebo was adjusted upward to conserve an overall significance level of 0.050.

Intent to Treat Analysis

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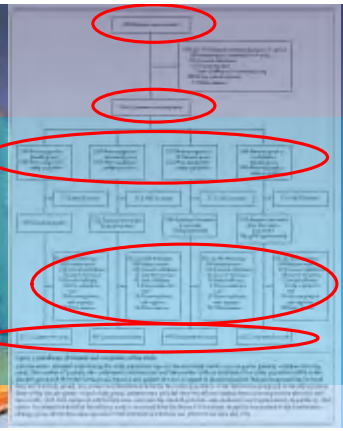

Recruitment

Randomization

Assignment

40% Withdrew (why?)

Completion

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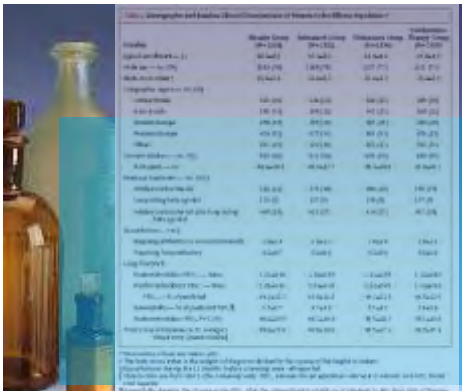

Similar to each other going in

65 yo M

BMI 25

23% USA

50 pack years

FEV 1 = 44

3.7% reversible

1/3 prior CS+BA

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The steering committee, made up of six academic investigators and two employees of the sponsor, developed the design and concept of the study, approved the statistical plan, had full access to and interpreted the data, wrote the manuscript, and was responsible for the decision to publish the manuscript. An academic author wrote a draft of the manuscript; an employee of the sponsor performed the statistical analysis. The academic authors vouch for the veracity and completeness of the data and the data analysis. The sponsor did not place any restrictions on the academic authors regarding statements made in the final manuscript.

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Demographic and baseline clinical characteristics of the efficacy population are shown in Table 1. The mean age was 65 years, and the mean value of postbronchodilator FEV_1 was 44% of the predicted value. During the year before entry into the study, more than half the patients had used inhaled corticosteroids, a long-acting beta-agonist, or both, and 57% of the patients had reported an exacerbation. The proportion of patients who withdrew from the study was significantly higher in the placebo group (44%) than in the three other groups, and the proportion was lowest in the combination-therapy group (34%) (Fig. 2A). The total number of years of exposure to the study drugs was 3678 in the combination-therapy group, 3258 in the placebo group, 3499 in the salmeterol group, and 3533 in the fluticasone group. The rate of adherence to treatment was similar in all groups, ranging from 88% to 89% of the prescribed doses taken.

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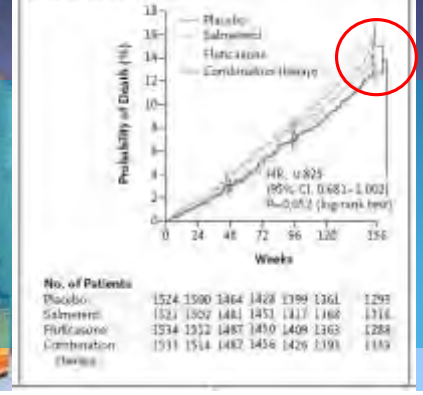
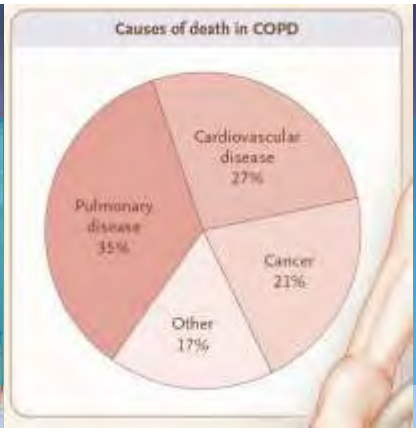
MORTALITY

Vital status was known at 3 years for 6111 of the 6112 patients included in the efficacy population. There were 875 deaths within 3 years after randomization. The proportions of deaths from any cause at 3 years were 12.6% in the combination-therapy group, 15.2% in the placebo group, 13.5% in the salmeterol group, and 16.0% in the fluticasone group. The absolute risk reduction for death in the combination-therapy group as compared with the placebo group was 2.6%, and the hazard ratio was 0.825 (95% confidence interval [CI], 0.681 to 1.002; P=0.052), corresponding to a reduction in the risk of death at any time in the 3 years of 17.5% (95% CI, −0.2 to 31.9% [all adjusted for the interim analyses) (Fig. 2B and Table 2).

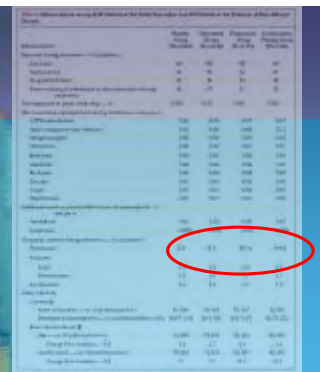




EXACERBATIONS, HEALTH STATUS, AND LUNG FUNCTION

According to our statistical models, the annual rate of exacerbations was 0.85 (95% CI, 0.80 to 0.90) in the combination-therapy group and 1.13 (95% CI, 1.07 to 1.20) in the placebo group, resulting in a rate ratio for exacerbations of 0.75 (95% CI, 0.69 to 0.81; P<0.001), which is a reduction of 25% and corresponds to a number needed to treat of four to prevent one exacerbation in 1 year. Annual rates of exacerbations in the salmeterol group and the fluticasone group were significantly lower than in the placebo group (Table 2). Overall, 26% of the patients were hospitalized at least once during the 3-year study period. Annual admission rates were 17% lower in the combination-therapy and salmeterol groups than in the placebo group (P≤0.03) (Table 2), corresponding to a number needed to treat of 32 to prevent one hospitalization in 1 year.

exacerbation of COPD. The probability of having pneumonia reported as an adverse event during the 3-year study period was significantly greater among patients receiving a study medication containing fluticasone propionate: the probability was 19.6% in the combination-therapy group, 12.3% in the placebo group, 13.3% in the salmeterol group, and 18.3% in the fluticasone group (P<0.001 for the comparison between both the combination-therapy and fluticasone groups and the placebo group). Among patients receiving study med-



pared with the placebo group, did not meet the predetermined level of statistical significance. Dur-

not achieve statistical significance. The first is that there is no effect of salmeterol plus fluticasone propionate on survival. In this scenario, the

mortality but that our study was underpowered to detect this effect. Our power calculations were

pated.[14,17] The TORCH study was designed to have 90% power to detect an effect of 4.3 percentage points on overall mortality; in practice, we identified a reduction of 2.6 percentage points. In addition, there was a high withdrawal rate, which was highest among patients in the placebo group.

The TORCH study recruited patients with COPD from around the world, and we think that our findings can therefore be generalized. The par-

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In Conclusion…

be viewed in this context. The potential for a reduction in the risk of death of 2.6 percentage points among patients treated with salmeterol plus fluticasone propionate, as compared with placebo, and the 17.5% reduction in the risk of death that was identified in the study clearly merit further investigation in future large, prospective trials. Until such trials are completed, our data support the use of salmeterol plus fluticasone propionate in the clinical management of COPD.

Supported by GlaxoSmithKline.

Dr. Calverley reports receiving consulting fees from AstraZeneca, GlaxoSmithKline, Pfizer, and Hoffmann–La Roche, speak-

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Combination therapy, as compared with monotherapy with long-acting beta-agonists or inhaled corticosteroids, offers statistically significant advantages for health status, frequency of exacerbations, use of oral steroids, and — probably most important clinically — protection against a decline in lung function. This finding confirms the position of combination therapy in current guidelines for the treatment of patients with COPD that recommend its use for those with severe COPD with frequent exacerbations[1] but not for patients with milder disease or without frequent exacerbations. Caution in the use of combination therapy is urged because of the finding in the TORCH trial of an increased rate of pneumonia among all patients receiving treatment containing inhaled corticosteroids. This finding urgently requires further investigation, and I urge the sponsor of this study to undertake a large trial to determine its importance.

Editorial

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Having read, re-consider

- Intrinsic vs Extrinsic Validity
  - Intrinsic:
    - Did the study really prove what it set out to and reported to prove (was it a "good" study)
  - Extrinsic:
    - Which "real-world" patient population can this result be appropriately applied to and how will it change my practice (if at all)

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Another Approach?

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