# Thoughts on Multimodal Therapy for CNS Disease

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# Caveats

- These are general thoughts and do not represent deep expertise in neuroscience
- You have real CNS experts from FDA in your midst—they can correct/place into context my thoughts
- These thoughts are not FDA policy, but do reflect the general direction of thinking from FDA leadership, including center directors

# Your Goals

- ✓ Explore advances in development of multimodal therapies
- ✓ Highlight disease areas where multimodal approaches particularly useful
- ✓ Methods for establishing efficacy and safety for multimodal therapy compared with monotherapy
- ✓ Regulatory issues
- ✓ Reimbursement issues
- ✓ Lessons learned from other therapeutic areas

# Multimodal Therapy is likely the right way to think about treatment

- Complex, chronic diseases
- Primary etiology often will have multiple involved pathways with regulatory and counter-regulatory systems
- Magic bullet therapy unlikely

# What are the Obstacles?

- Difficulty evolving from a view that therapeutic evaluation must be a highly controlled experiment focused on precise measurement rather than a broader experiment based on principles of quality by design
- Concern that treatment interactions may impede commercial interests or claims
- Scale

# Development of Therapeutics

- Very difficult to show that a treatment “works” at all
- This is first order of business and may require targeted population with limited integration with clinical practice to clearly generate a signal
- But then, transition to trials capable of addressing broader conditions of use that better reflect real-world settings and circumstances
- In short, if a therapy is to be used in a multi-modal environment, it makes sense that it should be evaluated in a multi-modal environment

# Labeling

- Most fundamental source of information about a medical product
- By regulation must contain critical prescribing information or instructions for use
- This information is best when it includes information about the population (including concomitant therapies)

# Practice Guideline

- Enables input of professional judgement about product use
- Provides clinical context and fills in gaps in evidence
- It would be wise for therapeutic developers to think about label, practice guideline and reimbursement criteria as the clinical development program is designed

# Atherosclerosis—Simple Case

- Final common pathways-atherosclerosis, thrombosis
- Primary risk factors: lipids, hypertension, smoking, diabetes, lack of exercise
- Antithrombotics not usually targeted to specific risk measurement
- Each treatment has a modest effect, but when the 4-5 key therapies are used together, the effect is dramatic

# CAD—Typical Patient

- Coronary stent (these days often drug eluting)
- Aspirin, statin, ACE-inhibitor, anti-hypertensives (usually more than one!)
- Often will have been treated with a biologic during procedure
- Behavioral intervention to improve diet and exercise routine

# Heart Failure Patient

- Diuretic, ACE inhibitor, beta blocker
- ICD, Bi-ventricular pacemaker
- Biologics used in case of transplant
- Exercise prescription
- Diet discretion

# Amiodarone or an Implantable Cardioverter-Defibrillator for Congestive Heart Failure

Gust H. Bardy, M.D., Kerry L. Lee, Ph.D., Daniel B. Mark, M.D., Jeanne E. Poole, M.D., Douglas L. Packer, M.D., Robin Boineau, M.D., Michael Domanski, M.D., Charles Troutman, R.N., Jill Anderson, R.N., George Johnson, B.S.E.E., Steven E. McNulty, M.S., Nancy Clapp-Channing, R.N., M.P.H., Linda D. Davidson-Ray, M.A., Elizabeth S. Fraulo, R.N., Daniel P. Fishbein, M.D., Richard M. Luceri, M.D., John H. Ip, M.D. and the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) Investigators

N Engl J Med
Volume 352;3:225-237
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The NEW ENGLAND JOURNAL of MEDICINE

# Study Overview

- This placebo-controlled study compared the effect of amiodarone and an implantable cardioverter-defibrillator (ICD) on mortality in patients with New York Heart Association class II or III congestive heart failure (CHF)
- Amiodarone had no benefit overall and slightly increased mortality among patients with class III CHF
- ICD therapy reduced mortality overall, but the benefit appeared to be restricted to patients with class II CHF
- These important results will broaden the use of ICD therapy

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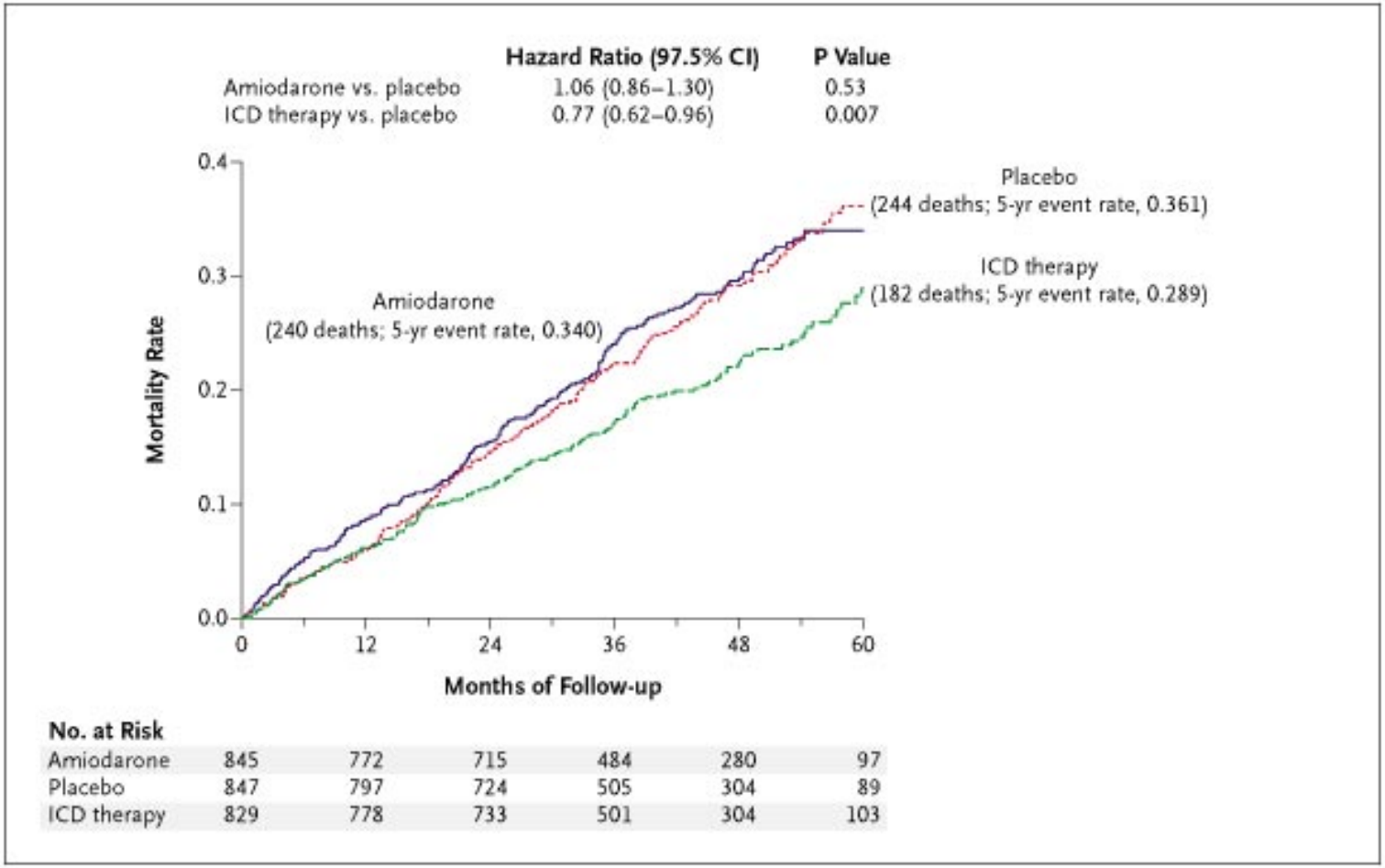
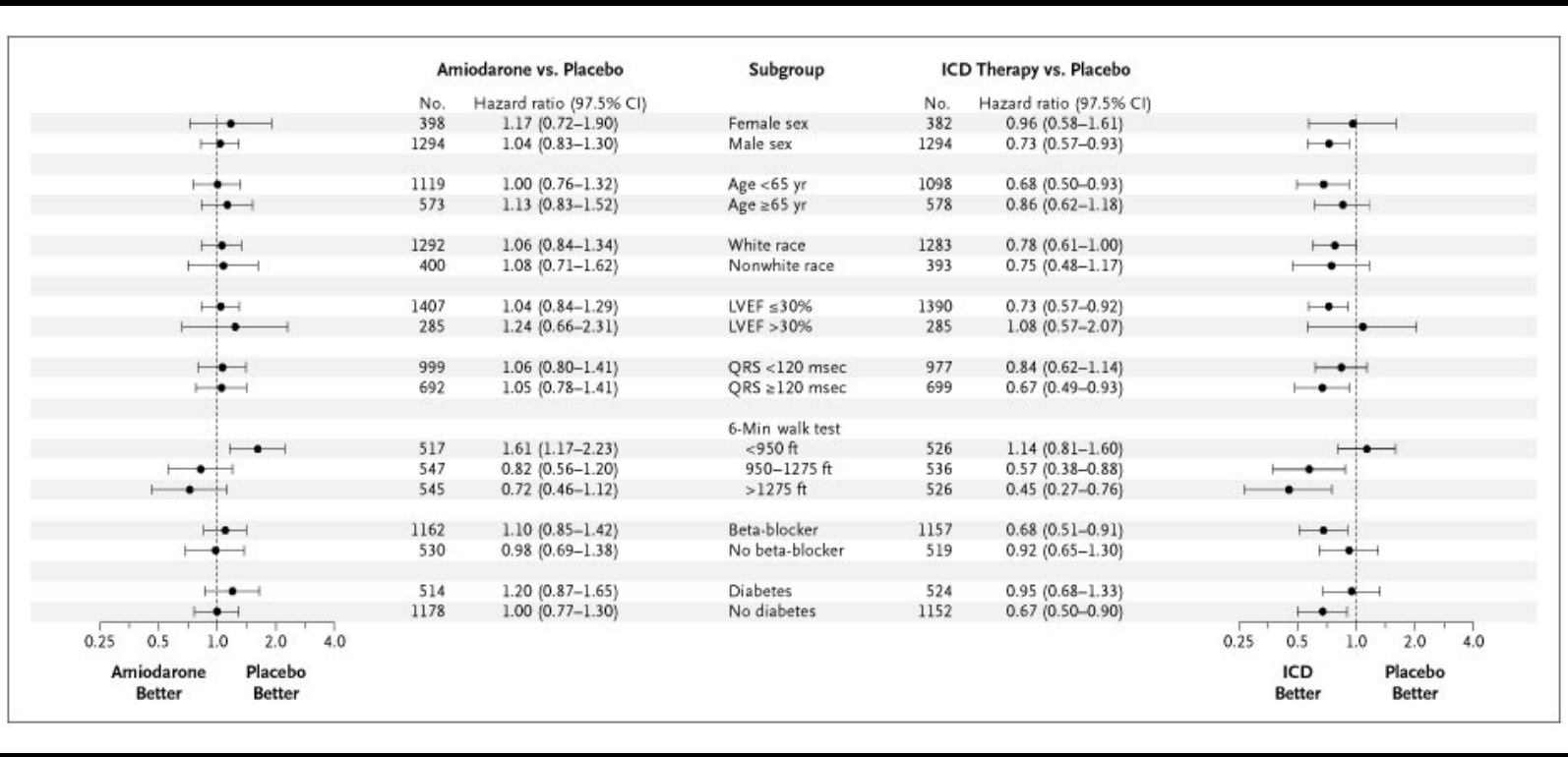
# Kaplan-Meier Estimates of Death from Any Cause




Bardy, G. et al. N Engl J Med 2005;352:225-237

# Hazard Ratios for the Comparison of Amiodarone and ICD Therapy with Placebo in Various Subgroups of Interest




Bardy, G. et al. N Engl J Med 2005;352:225-237

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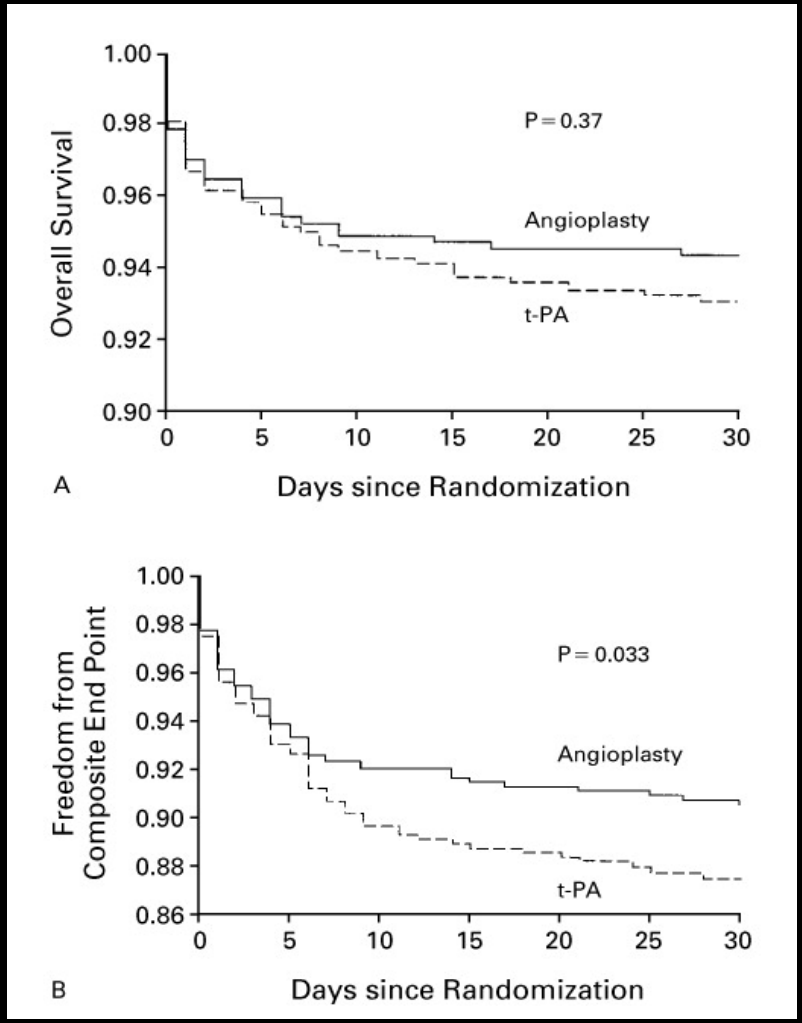
# Conclusions

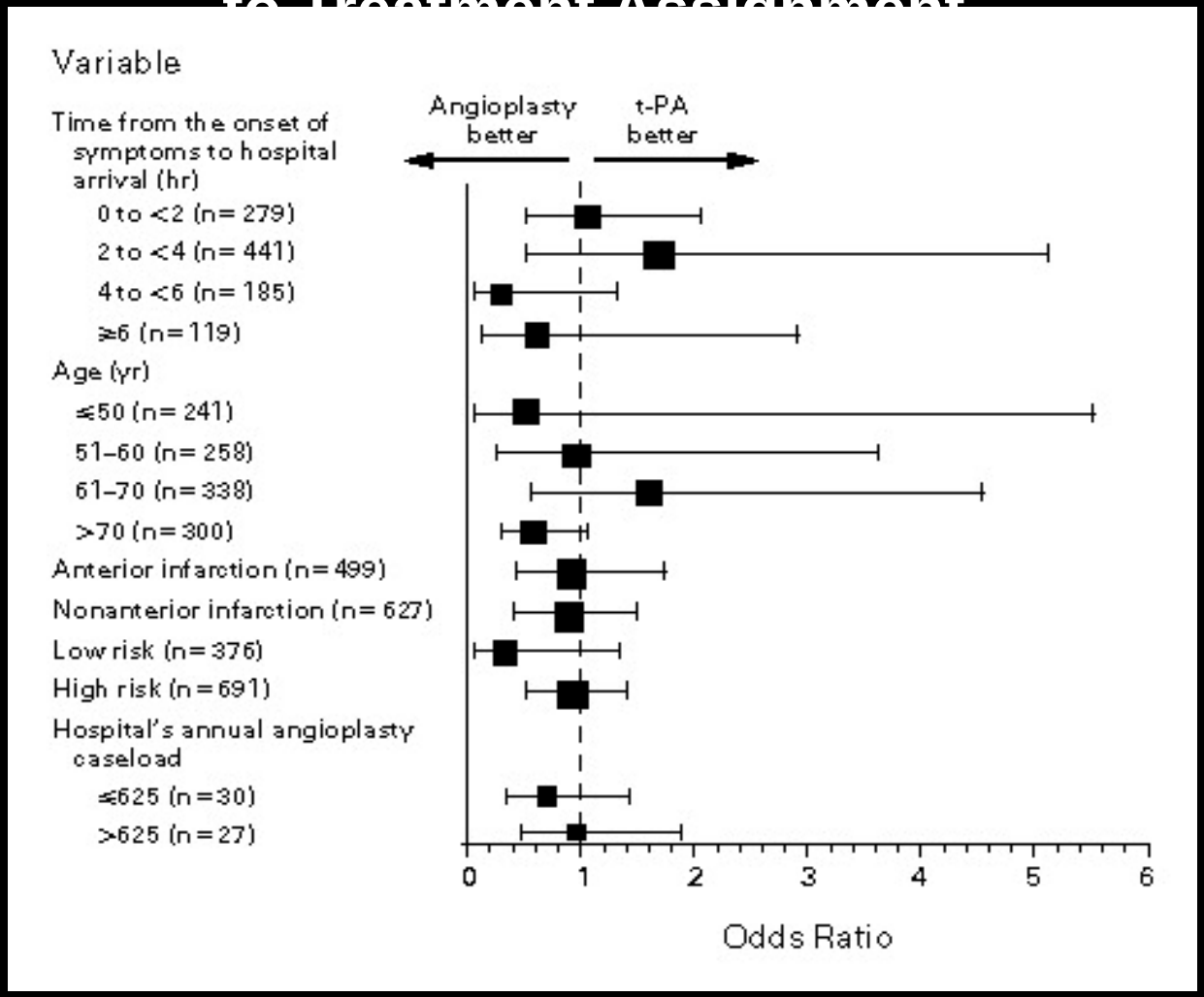
- In patients with NYHA class II or III CHF and LVEF of 35 percent or less, amiodarone has no favorable effect on survival, whereas single-lead, shock-only ICD therapy reduces overall mortality by 23 percent

**Kaplan–Meier Curves for Survival (Panel A) and Freedom from the Composite End Point of Death, Reinfarction, and Disabling Stroke (Panel B) in the Study Patients within the 30 Days after Randomization, According to Treatment Group.**




**The Global Use of Strategies to Open Occluded Coronary Arteries in Acute Coronary Syndromes (GUSTO IIb) Angioplasty Substudy Investigators. N Engl J Med 1997;336:1621-1628.**

# Point Estimates and 95 Percent Confidence Intervals for the Odds Ratios for Death within 30 Days in Several Prospectively Defined Subgroups of Patients, According to Treatment Assignment

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# When it comes to Combinations…

- The big picture is that in most chronic diseases therapy is multimodal
- There is a narrowly defined universe of combination products that fall under regulations specifically as combinations, requiring collaboration across product types
- But it may be useful to think in general principles as well as specific regulations

# Combination products come in three basic configurations

- they can be physically or chemically combined;
- they can be  co-packaged
- they can be separately distributed with specific labeling that provides instructions for their combined use

# Issues in Combination Product Regulation

- different user fees
- different evidentiary standards for different application types,
- different manufacturing standards.
- Different cultures in the product centers

# Goals: Combination Products

- modernize and adapt our system,
- increase efficiency, consistency, and predictability in our review of these combination products,
- so that we continue to encourage innovation and support the development of these vital technologies

# Combination Products Improvement

- Lean management approach to optimizing the process, including consults between centers
- Development of IT systems to support the process
- Combination Products Council, chaired by experienced leader, bringing together Center leadership to resolve tough issues and develop principles

# Human Factors Studies

- **Human factors studies are an important piece of how we evaluate these products. We need to study and learn how people interact with technology, and to understand how the design of that interaction affects the quality, experience, and outcomes of that interaction.**

# Human Factors Studies

- Human factors evaluations are a central consideration for FDA when it assesses combination products, particularly those that include certain devices, since the design of a combination product can have a significant impact on whether a given product is safe and effective for its intended use.
- Earlier this year, FDA published draft guidance for industry and FDA staff titled “Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development.”
  - This draft guidance builds on principles articulated in earlier guidances that discuss human factors and medication error considerations for medical devices and drugs.
  - When final, it will represent FDA’s thinking on when and how combination product manufacturers should perform human factors evaluations for investigational or marketing applications.

SCALE!

# The President's Precision Medicine Initiative (PMI)


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President Barack Obama

January 30, 2015