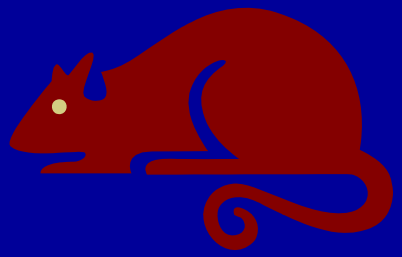
Defining Surrogacy: a Regulatory Perspective

Aliza Thompson, MD
Medical Officer
Division of Cardiovascular and Renal Products, FDA

Proteinuria in drug development

Safety



Animal	Finding
Rat	Renal tubular necrosis
Dog	Proteinuria, hematuria, hypoalbuminemia

Proteinuria in drug development

Selecting an at-risk population

Study	Baseline proteinuria	N	Follow-up	ESRD, death, doubling Cr
RENAAL		Losartan=751 Placebo=762	3.4 years	↓ RR
IDNT		Irbesartan=579 Placebo=569	2.6 years	↓ RR

Outline

- Establishing efficacy from a regulatory perspective: the use of surrogates
- Proteinuria as a surrogate in chronic kidney disease

Disclaimer

The views expressed in this talk represent my opinions and do not necessarily represent the views of the FDA.

Establishing efficacy from a regulatory perspective

- "Substantial evidence" and "Adequate and well-controlled" trials

  -1962 Kefauver-Harris Drug Amendment

- Effect must be clinically meaningful (added by court)

  - 1986 Warner-Lambert v Heckler

Establishing efficacy from a regulatory perspective

Clinically meaningful endpoints

- Important Outcome: *e.g., death, need for dialysis*
- Symptom
- Surrogate: *"a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful endpoint that is a direct measure of how a patient feels, functions, or survives and is expected to predict the effect of the therapy"*

Temple R. Are surrogate markers adequate to assess cardiovascular disease drugs? JAMA .1999; 282 (8):790-795.

How the Agency uses surrogates

- **Accepted surrogates** (e.g., BP, doubling sCr): as the definitive endpoint in the phase 3 clinical trials that establish drug efficacy

- **Surrogates that are "reasonably likely" to predict clinical benefit** (Subpart H/E): accelerated approval of a drug for a serious or life-threatening illness that comes with post-marketing commitment to complete studies verifying its clinical benefit

How the Agency uses surrogates

Still need sufficient data on **safety** of drug:

- Can't tolerate much risk if the benefit is only hypothetical.
- Might be the dominant factor in the size of the development program (as it is for anti-hypertensives).

Proteinuria as a surrogate

Proteinuria as a surrogate

Dramatic change in proteinuria or albuminuria (e.g. showing change from macroalbuminuria to normoalbuminuria) and that effect persists when hemodynamic effect is gone.

Proteinuria as a surrogate

Persistence of effect on proteinuria after drug withdrawal is critical→ it makes proteinuria into a more direct measure of an anatomical change.

Proteinuria as a surrogate

- As a component of definition of renal remission and renal flare in lupus nephritis.
- As part of Subpart H/E approval. Must be feasible to complete post-marketing commitment to perform study that verifies clinical benefit (best case: study fully enrolled, active treatment completed and only long term follow-up needed).

Evaluating surrogates

Biologic plausibility	*Key consideration: Is it on the causal pathway to the clinical outcome of interest?*
Epidemiologic data	*Is there a consistent association between the surrogate and clinical outcome of interest?*
Data from intervention trials	*Does the surrogate reliably predict the effect of pharmacologically distinct agents or distinct interventions on a clinical outcome of interest?*

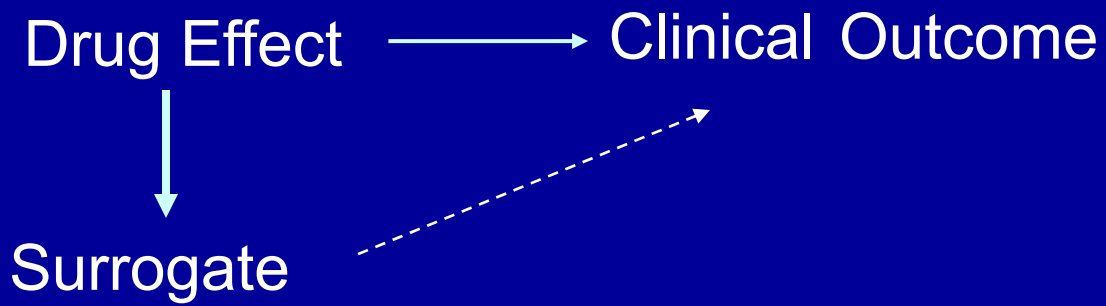
Proteinuria as a surrogate

Biologic plausibility	*Proteinuria is not a necessary intermediate on the causal pathway (in contrast to creatinine!)*
Epidemiologic data	*Abundant data, mostly supportive*
Data from intervention trials	*Data currently limited to a few intervention trials with ARBs/ACEI (RENAAL, IDNT, captopril study)*

Why does it matter that proteinuria isn't a necessary intermediate?

Ideal

Not Ideal



Scenarios possible in which effect on surrogate/intermediate endpoint may not predict effect on clinical outcome.

Why aren't epidemiologic data enough????

The Cardiac Arrhythmia Suppression Trial

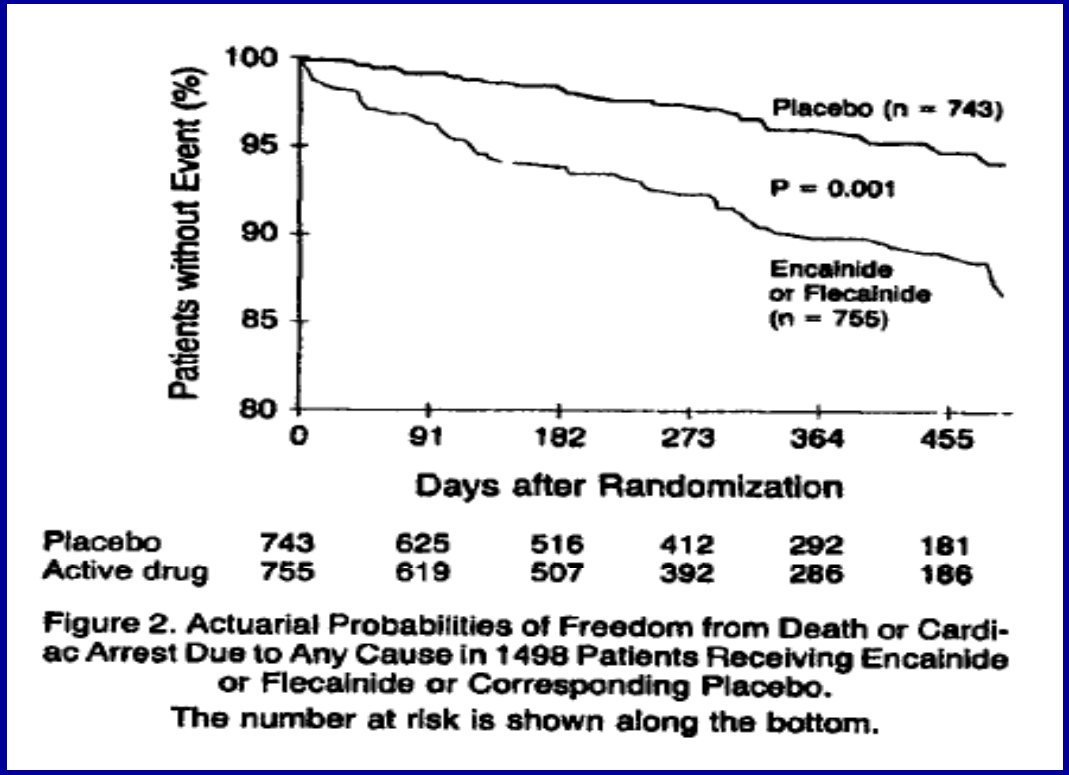


Figure 2. Actuarial Probabilities of Freedom from Death or Cardiac Arrest Due to Any Cause in 1498 Patients Receiving Encainide or Flecainide or Corresponding Placebo.
The number at risk is shown along the bottom.

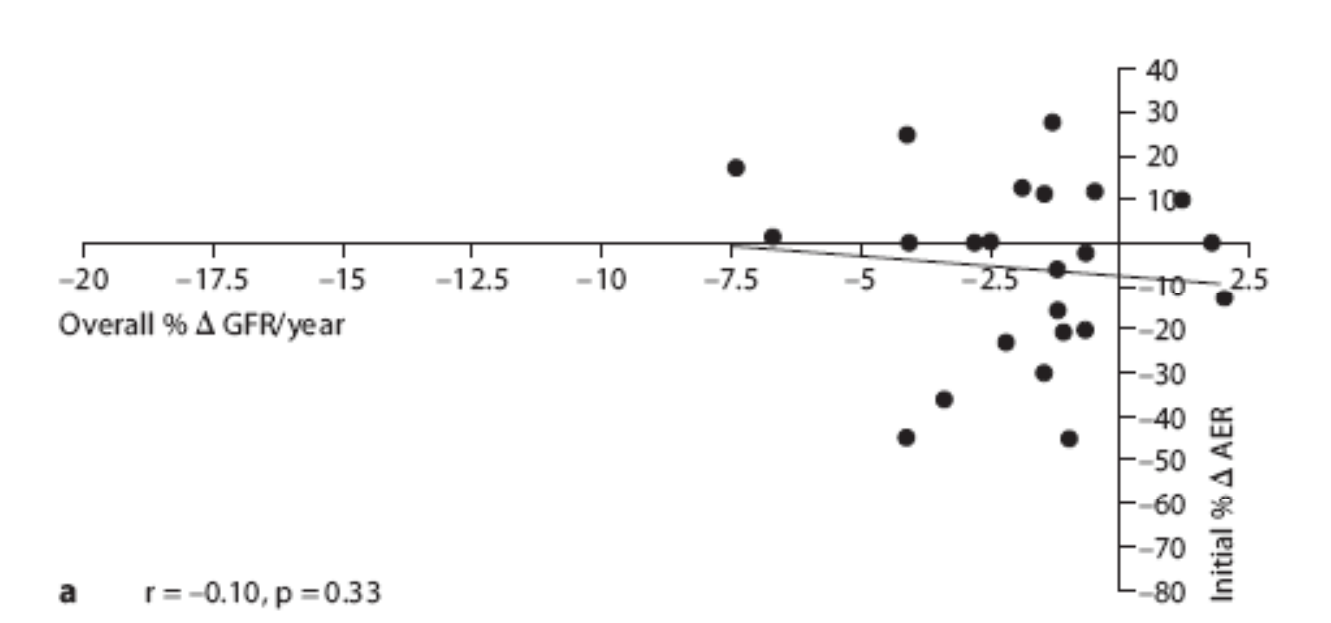
Echt DS, Liebson PR, Mitchell LB et al. Mortality and morbidity in patients receiving encainide, flecainide or placebo. The Cardiac Arrhythmias Suppression Trial. NEJM. 1991; 324(12): 781-788.

Other limitations

- Data from recent interventional trials (e.g. ONTARGET) raise questions about ability of small changes to predict effect on renal outcomes.
- Inconsistent association between changes in albuminuria and GFR.
- Inconsistency in relationship between reduction in proteinuria and magnitude of effect on clinical outcome.

Association between reduction AER and GFR

Response to antihypertensive therapy in nine trials (23 study groups) in subjects with early type 1 diabetic nephropathy



Source: Jerums G et al. Lowering of Proteinuria in Response to Antihypertensive Therapy Predicts Improved Renal Function in Late but Not in Early Diabetic Nephropathy: A Pooled Analysis. Am J Nephrol 2008;28:614–627.

Association between reduction proteinuria and clinical endpoints

Drug	% > Reduction in Proteinuria[a]	RR for Primary Endpoint
Captopril	28%	50.5%
Losartan	26%	16%
Irbesartan	26%	20%

a. 24-month data as available

Source: 2002 slide presentation, Dr. Douglas Throckmorton

Next steps

- More data from controlled outcome studies of pharmacologically distinct agents/distinct interventions demonstrating that changes in proteinuria reliably predict clinical outcomes of interest
- A context-limited approach to assessing proteinuria as a surrogate: assess performance within the context of specific kidney diseases and/or specific drug class → adoption as a surrogate in that context
- Explore predictive ability of various definitions of “dramatic changes” in proteinuria (recent data raise questions about predictive ability of small changes)

Developing drugs for CKD

- Enrich study population for patients likely to progress
- Address other important clinical manifestations of disease (nephrotic syndrome)
- Use effect on proteinuria as supportive of efficacy

Thanks.