Clinical Development of Biomarkers: Lessons Learned in CVD

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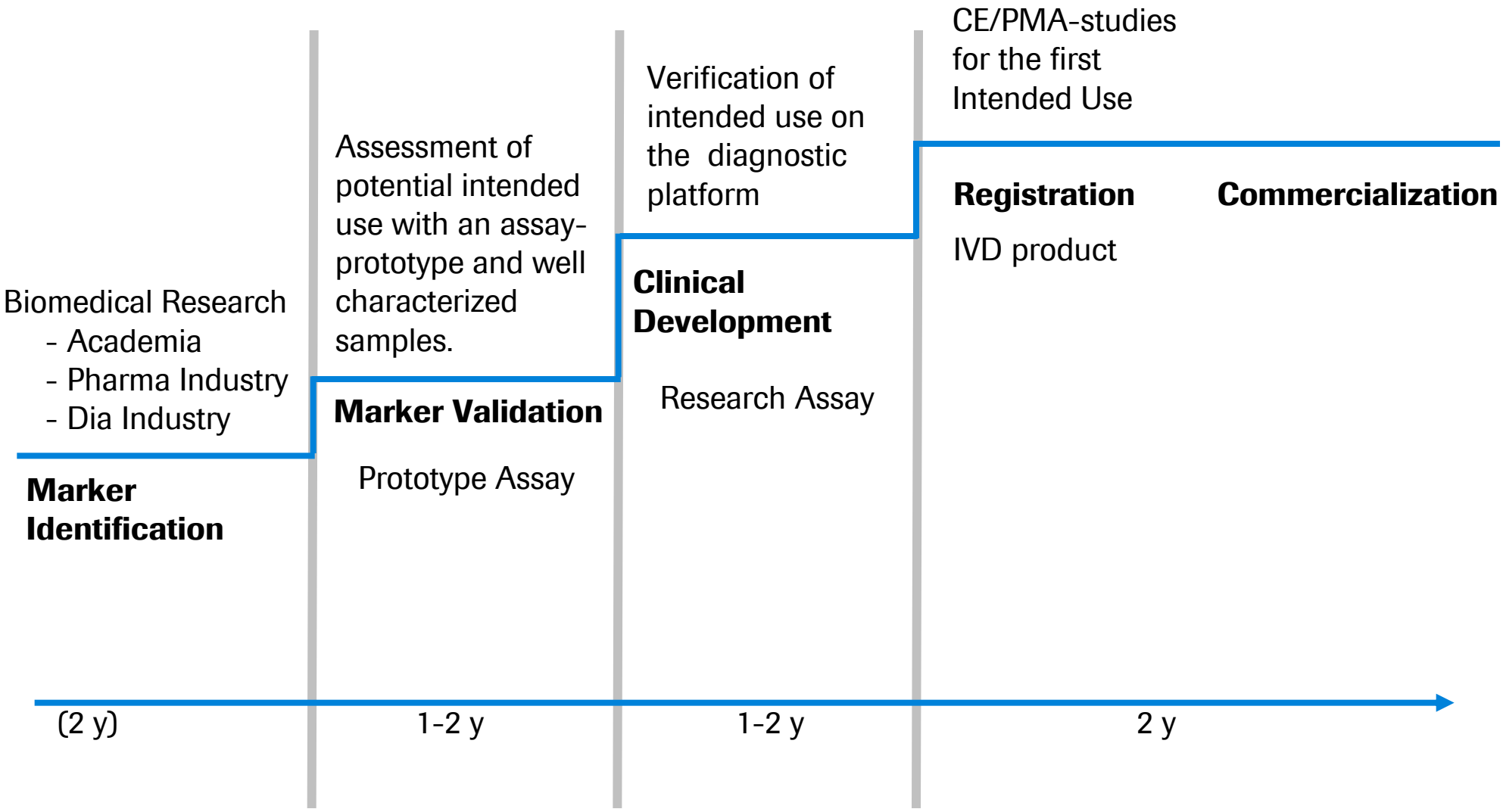
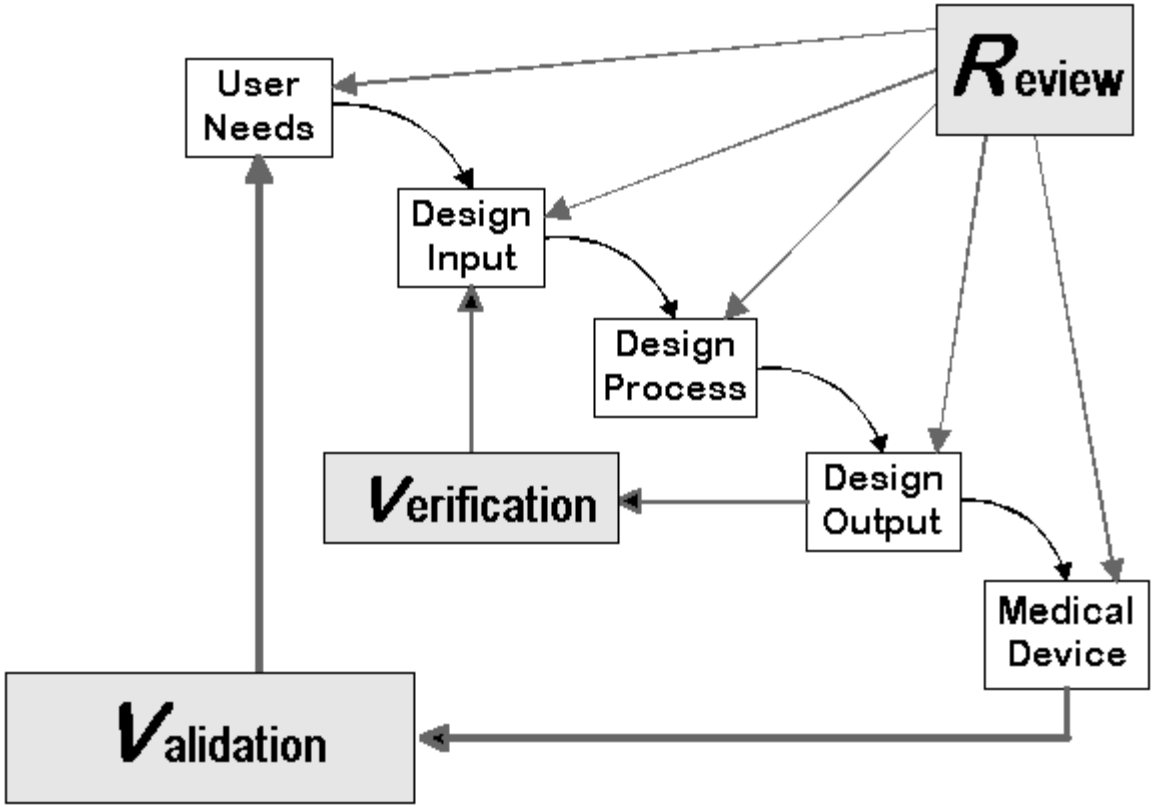
Novel In Vitro Diagnostic Development



IVD challenges

- Sample selection and access
- Broad antibody assessment vs. assay-specific antibody development
- Robustness assurance program:
  - Performance under “routine use“ conditions
- Transfer of manufacturing (production, standardization & QC) into operations of rare reagents (antibody conjugates) and kit components (reagent, calset, controls)
- Production and reference standardization (→ controlled lot-to-lot variability; <5%)
- Design verification and validation (incl. external studies under routine conditions) **before** the assays are used in phase III studies for clinical use validation

FDA Design Control Guidance For Medical Device Manufacturers



http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm070627.htm

Challenges to Demonstrating Clinical Utility

In order to influence outcomes,

A diagnostic must:

- Be ordered
- Be performed
- Be reported in a timely manner
- Be appropriately interpreted
- Influence a clinical ***decision***

  … that leads to an ***intervention***

  … ***consistently enough*** to clearly link to outcomes

A therapeutic must:

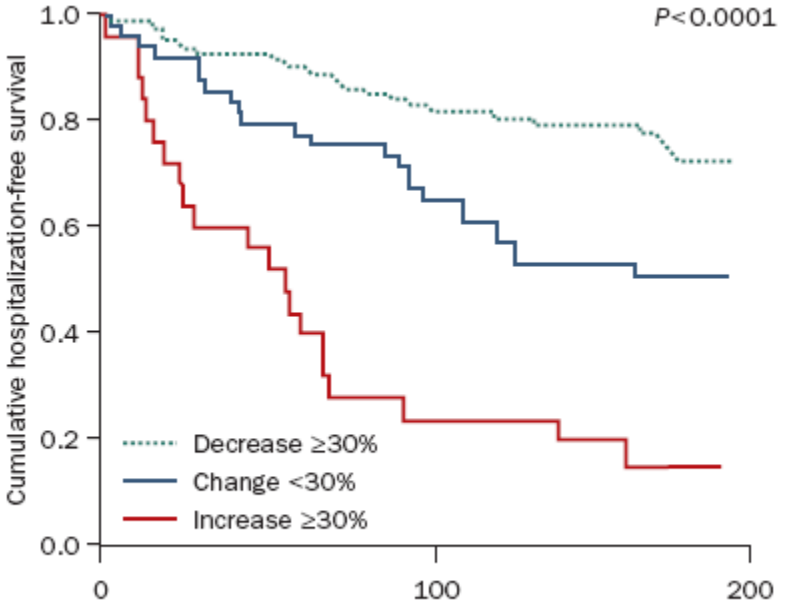
Be administered

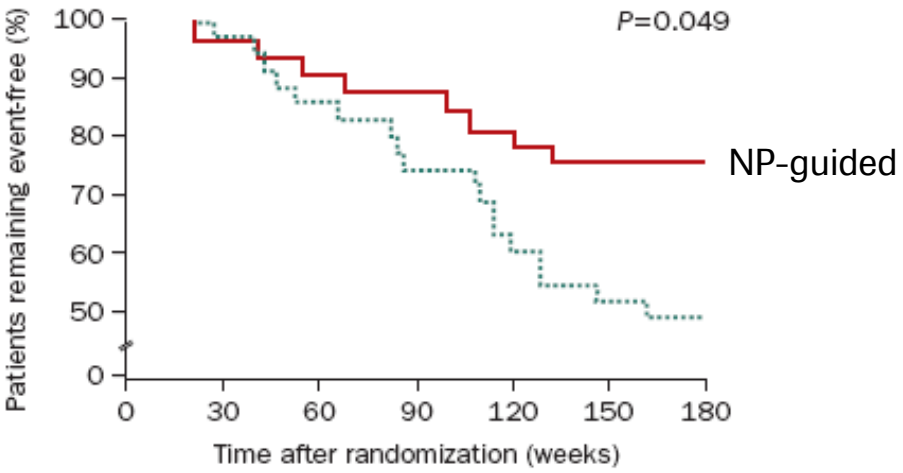
Natriuretic Peptides

From diagnosis of CHF to guiding therapy

Heart failure (CHF)

- Over 5% of healthcare spending (in US est. $35 bn[1])
- More costly than cancer
- Symptoms unspecific



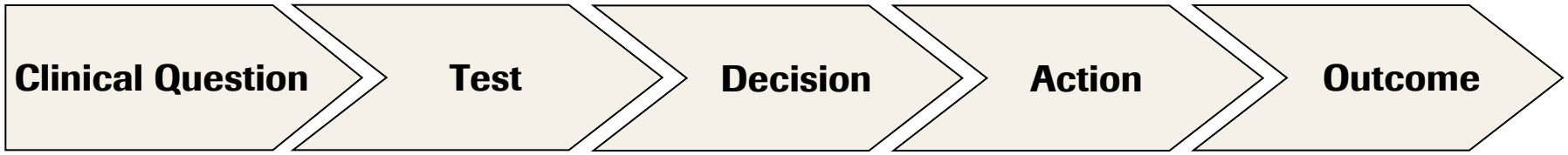


2008 AHA Statistical Update

Nat. Rev. Cardiol. 2010: 7, 13–20

Developing the Evidence

Why clinical evidence for diagnostics is harder

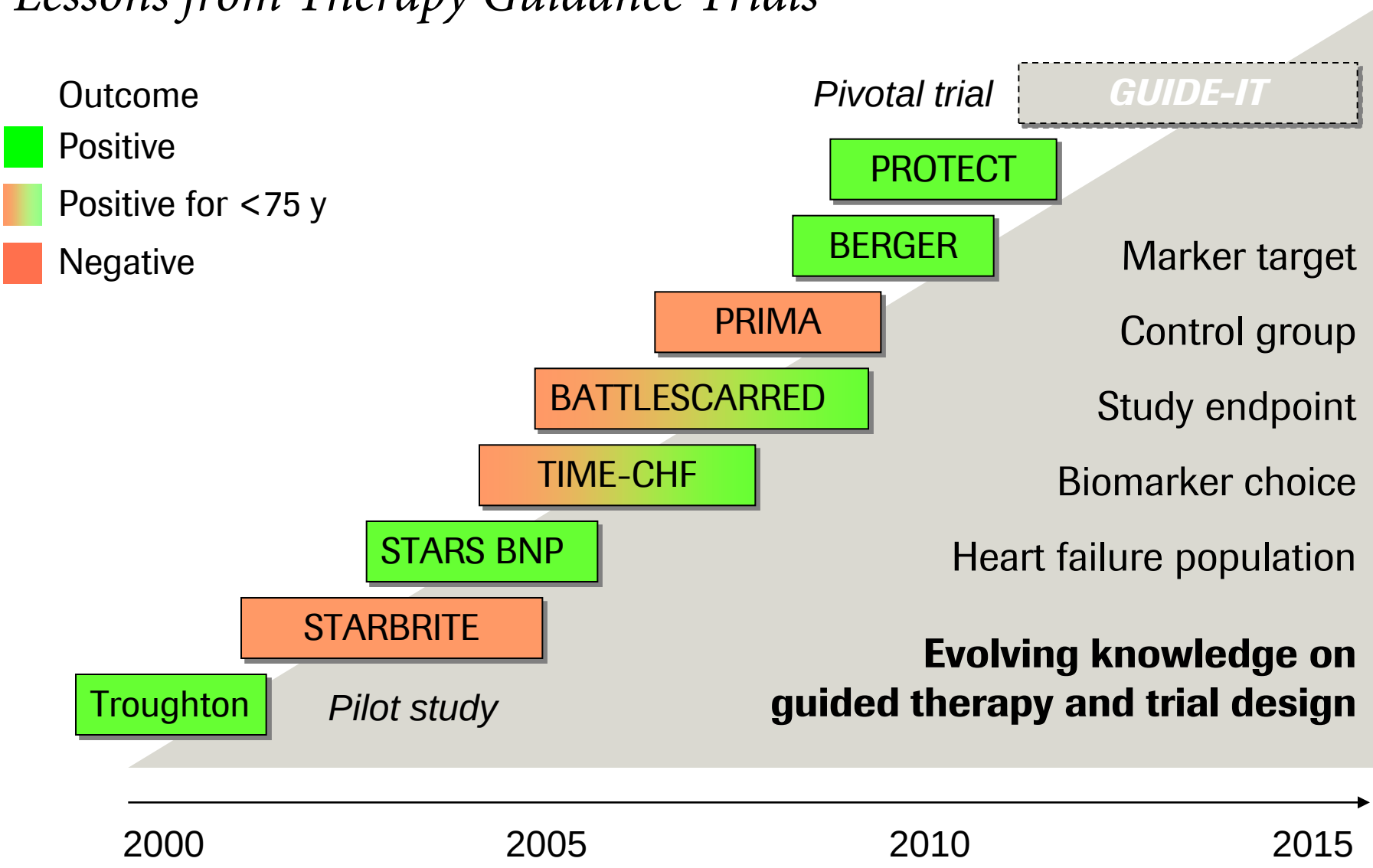


Clinical Question:

- Do natriuretic peptide levels contribute to improved outcomes in outpatient HF management?

NP-Guided Heart Failure Therapy

Lessons from Therapy Guidance Trials



Natriuretic Peptide Guided Heart Failure Therapy

Data Support

	Troughton	STAR-BRITE	STARS-BNP	TIME-CHF	BATTLE-SCARRED	PRIMA	PROTECT	Berger
n	69	137	220	499	364	345	151	278
Marker	NT-BNP	BNP	BNP	NT-BNP	NT-BNP	NT-BNP	NT-BNP	NT-BNP
Aim (pg/ml)	< 1692	< 2x dischar.	< 100	< 400 / 800	< 1270	Value at dischar.	< 1000	< 2200 algorith.
Control	HF score	Congest. score	Usual care	≤NYHA II	2 groups	Usual care	Standard of care	Usual + HF care
1° EP	CV Death, hosp.	hosp. free survival	HF death, HF hosp.	hosp. free survival	All-cause mortality	hosp. free survival	CV Death, HF hosp.	Death, HF hosp.
Age (y)	70	61	66	77	76	72	63	72
Male (%)	76	70	64	66	62	58	64	67
EF (%)	27	20	31	30	37	33	27	<40
IHD (%)	74	44	52	58	71	60	43	64
Ref.	Lancet 2000	Circulation 2006	JACC 2007	JAMA 2009	JACC 2010	JACC 2010	JACC 2011	JACC 2010

Outcome primary endpoint: positive | positive (<75 y) | negative

Natriuretic Peptides

From diagnosis of CHF to guiding therapy

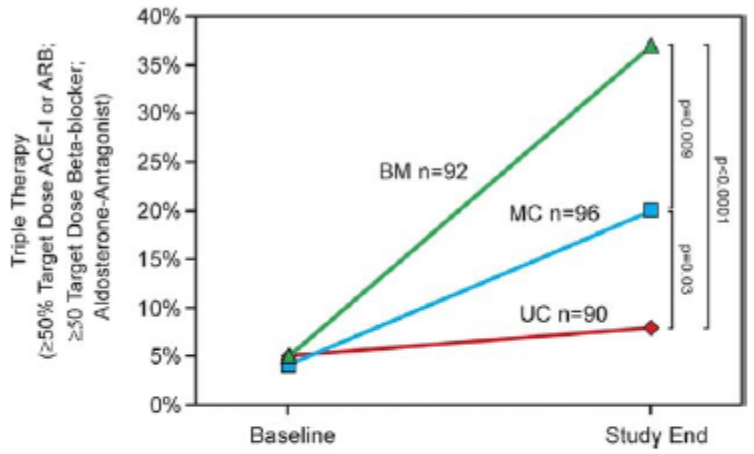


Figure 3 **Effect of UC, MC, and BM on Heart Failure Therapy**

The proportion of triple therapy (spironolactone and ≥50% of the target dose of an angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and of a beta-blocker) was similar among groups at baseline, but was higher in the BM group versus the MC group, and higher in the MC versus the usual care (UC) group at follow-up. Abbreviations as in Figure 1.

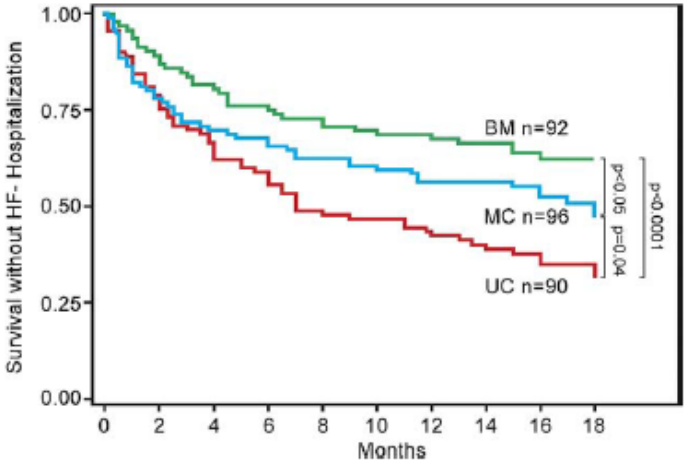


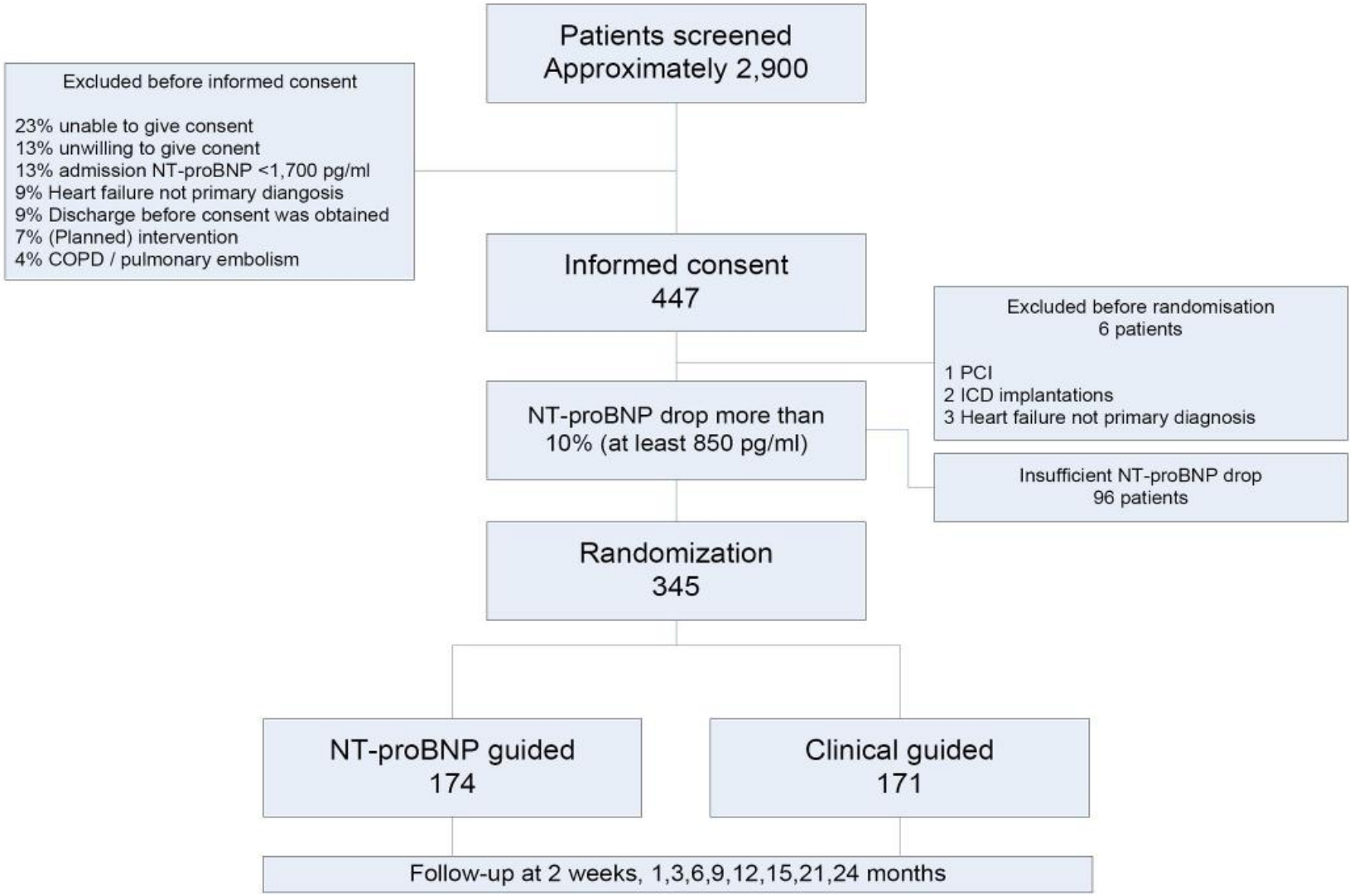
Figure 5 **Survival Without HF Hospitalization**

Up to 18 months, the combined end point of death or heart failure (HF) hospitalization was lower in the BM (37%) versus MC group (50%; $p < 0.05$) and in the MC versus UC group (65%; $p = 0.04$). Abbreviations as in Figures 1 and 3.

Berger, JACC 2010: 55, 7

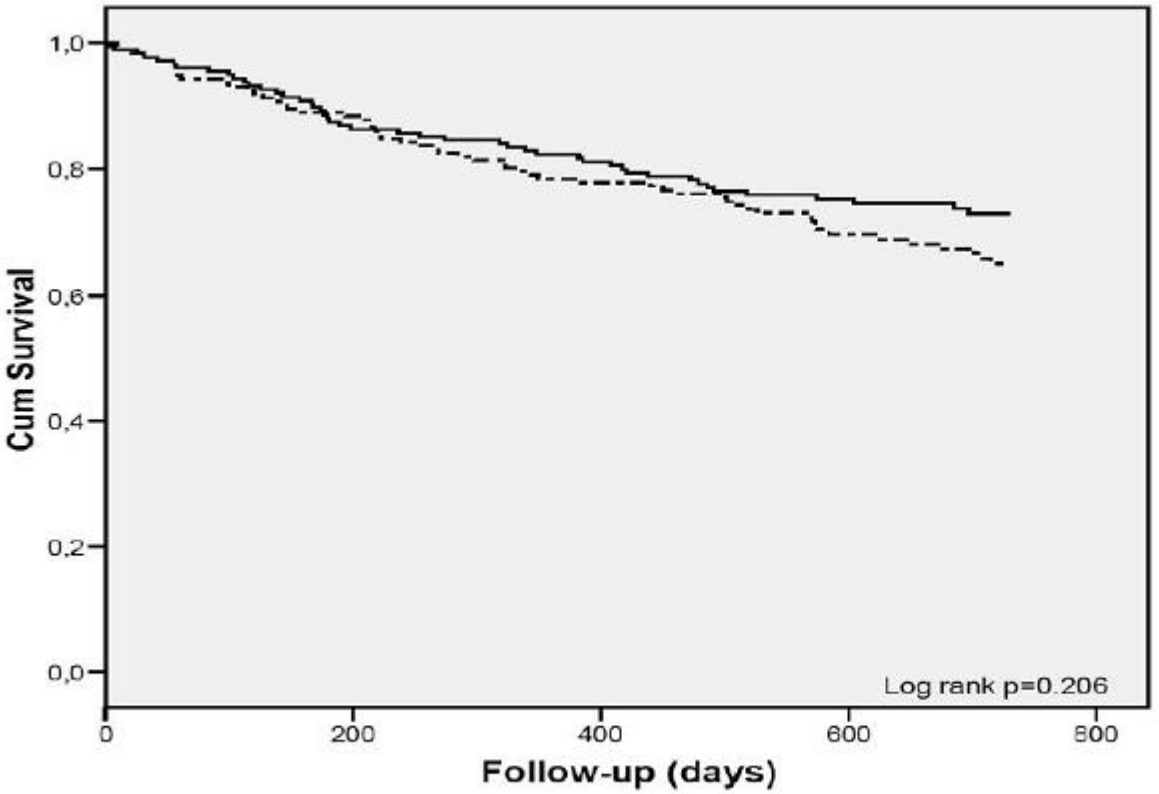
Example

A good concept…



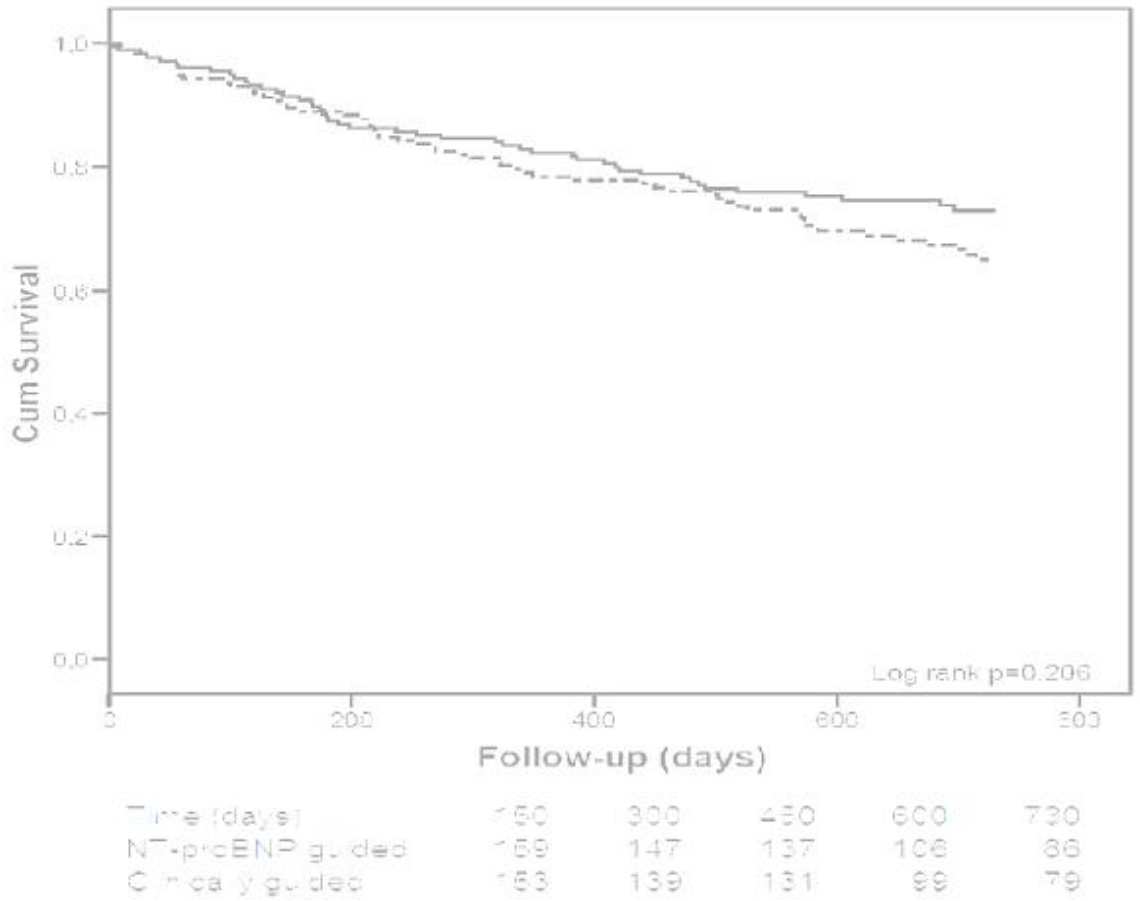
Primary endpoint

>20%, no impact



Time (days)	150	300	450	600	730
NT-proBNP guided	159	147	137	106	86
Clinically guided	153	139	131	99	79

Author's Conclusions:



- "No value to information"
- "… *simply increasing diuretics is often not enough…*"
- "Only value when there is room to add significant therapy…"

Developing the Evidence

Why clinical evidence for diagnostics is harder

Making the diagnosis is only the first step

- Still requires intervention in order to alter outcomes
- How to control the intervention?
- Do evidence requirements differ if the test is used for diagnosis or therapy selection?

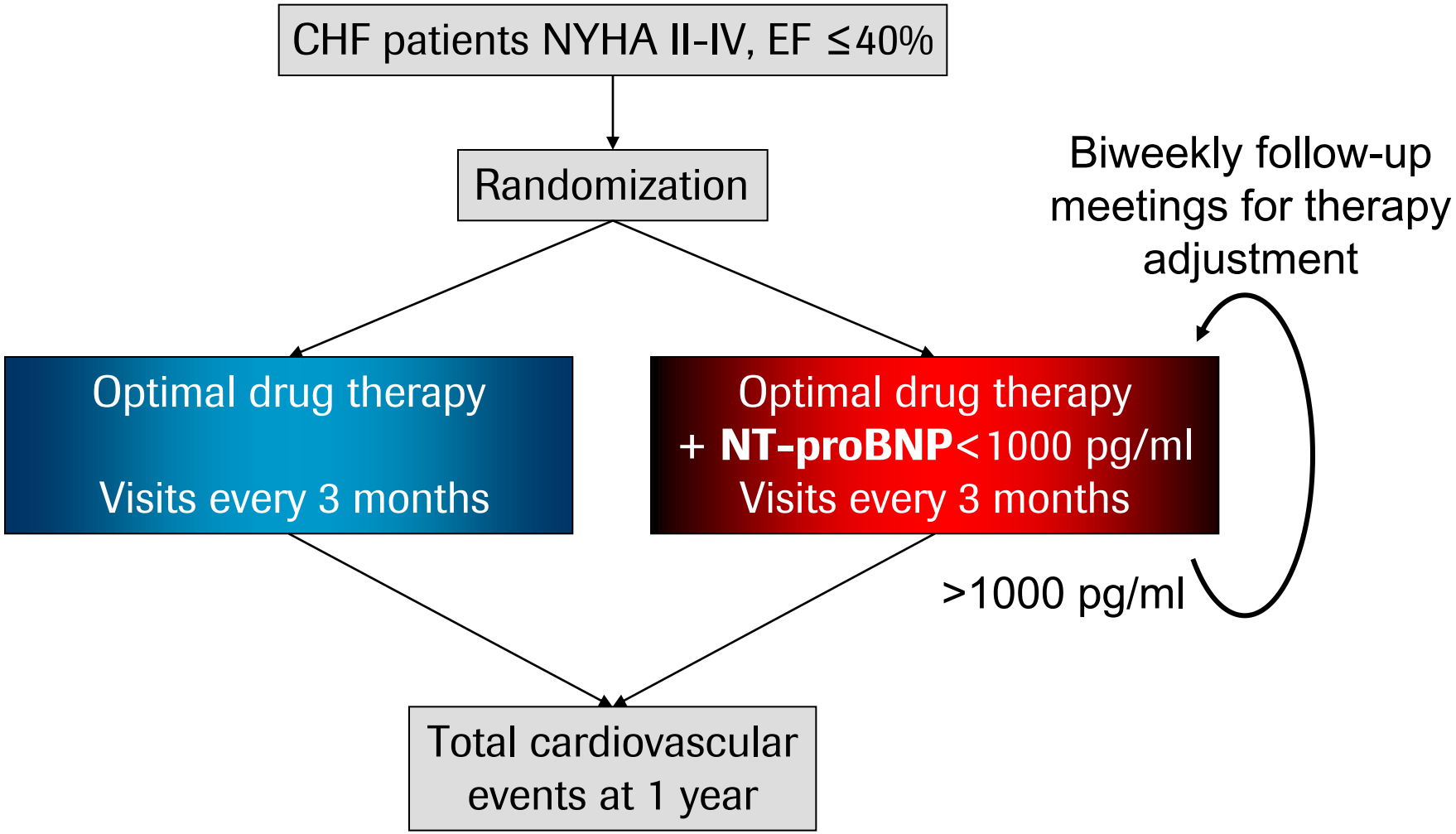
Developing the Evidence

Why clinical evidence for diagnostics is harder

In most cases, links to outcomes require an intervention

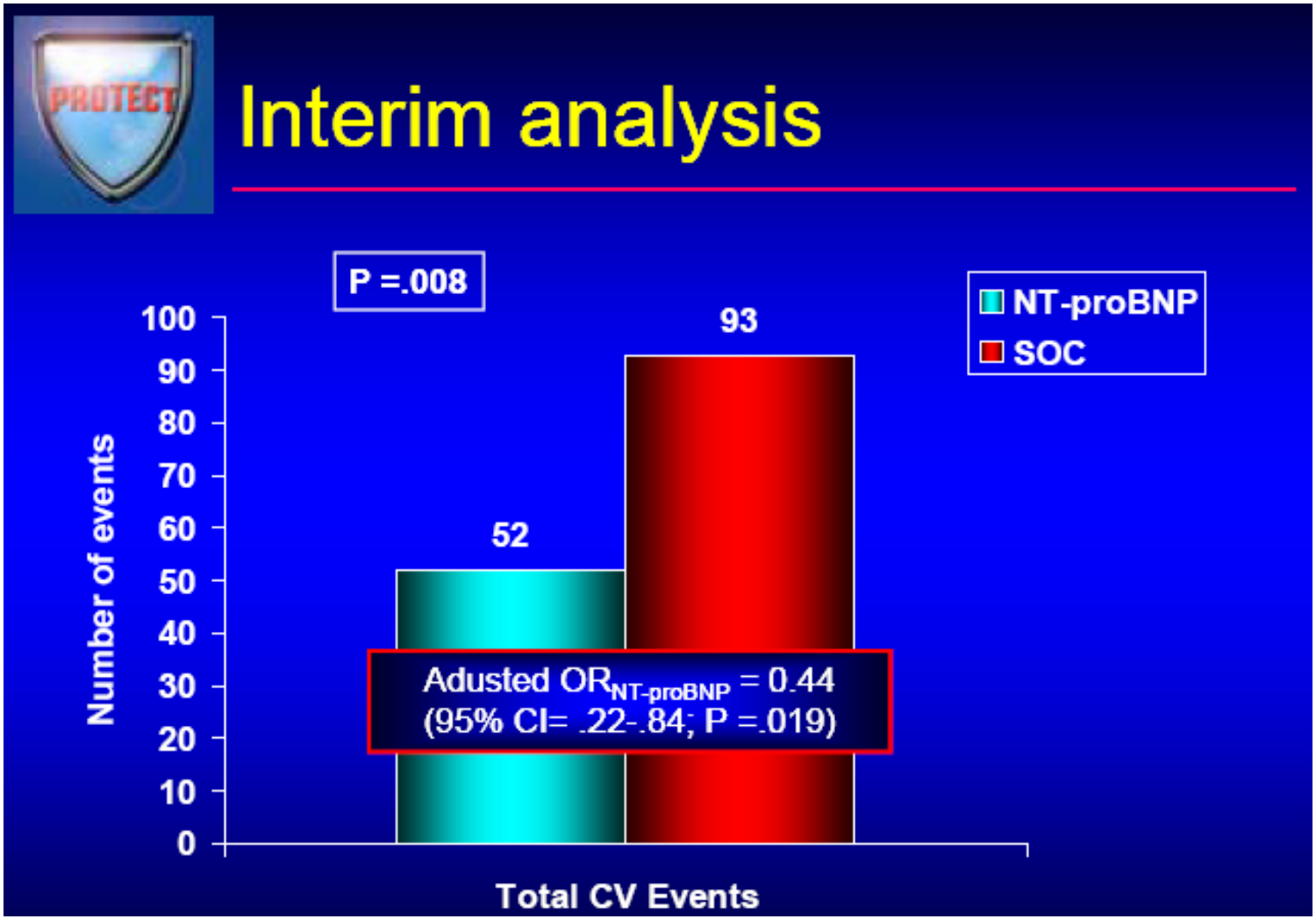
- Best evaluated as part of a ‘test and treat’ plan
- Test result must be acted upon for there to be any potential benefit

PROTECT Study Design



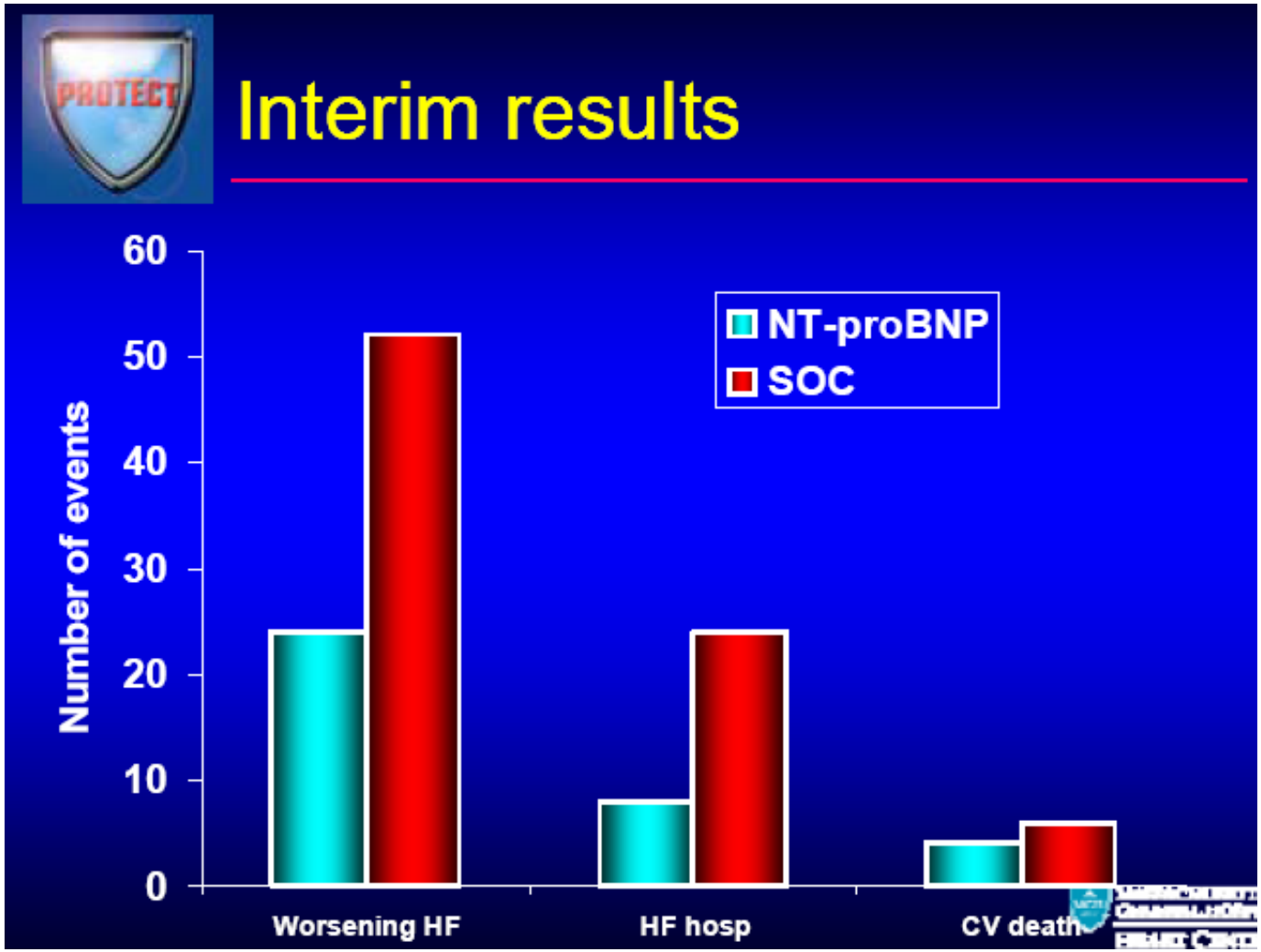
Bhardwaj Am Heart J

NT-proBNP Guided Heart Failure Therapy



From J. Januzzi, UNC Heart Failure Meeting 2010

NT-proBNP Guided Heart Failure Therapy



From J. Januzzi, UNC Heart Failure Meeting 2010

What Does it Take to Establish Morbidity and Mortality Benefits in Heart Failure?

Drug	Trial	Sample size
ACE inhibitor	SOLVD	2569
Beta blocker	MERIT-HF	3991
Angiotensin Receptor Blocker	Val-HeFT	5010
Nitrates-Hydralazine	AHeFT	1050
Direct Renin Inhibitor	Atmosphere	7041
NPs guidance		2300

Adapted from M. Felker, Duke Clinical Research Institute

What about regulatory oversight?

- A bad test is as harmful as a bad drug!
- Would you use a drug if:
  - *You aren't sure how it is formulated?*
  - *You don't have clinical data about how it should be used?*
  - *You don't have reliable efficacy data?*
- This is especially worrisome if crucial treatment decisions are made based on the test results (as in PM)

What about regulatory oversight?

Consider a risk-based approach:

- Tests that influence crucial treatment decisions deserve the highest level of scrutiny
- Tests that are used as part of a larger diagnostic algorithm can afford a lower level of scrutiny
- Results should not depend on the lab where the test is performed
  - “lab developed tests“ should receive the same degree of oversight as IVDs
- Reimbursement should reflect the level of evidence of performance, safety and clinical utility provided

Where we need more clarity:

- Newly discovered biomarkers and their application to existing drugs on the market (drug labeling changes)
- Companion diagnostics (“Personalized Medicines”) in general
- Appropriate use of data from observational studies and retrospective data
- New technologies

To Support Innovation in Diagnostics: Recommendations

- Increase research funds for studies to demonstrate clinical utility
  - Including industry-government partnerships
- Increase regulatory requirements on a risk-balanced basis
- Ensure a level playing field
- Increase reimbursement commensurate with increased data requirements (as for therapeutics)
  - Set incentives appropriately to reward innovation