NISS-Merck Meet-Up

Webinar

10 September 2019

To Be Or Not To Be
(A Subgroup)

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Bringing data to life.

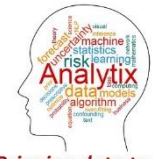
Acknowledgement

My thinking on this problem has been significantly influenced by former colleagues at Lilly, most notably

Lei Shen

Rick Higgs

Ilya Lipkovich



Alice in Wonderland

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Alice in Wonderland

Alice: "Would you tell me, please, which way I ought to go from here?"

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Alice in Wonderland

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Cheshire Cat: "That depends a good deal on where you want to get to."

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Alice in Wonderland

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Alice: "I don't much care where—"

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Alice in Wonderland

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Alice: "—so long as I get SOMEWHERE."

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Alice in Wonderland

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Alice: "I don't much care where—"

Cheshire Cat: "Then it doesn't matter which way you go."

Alice: "—so long as I get SOMEWHERE."

Cheshire Cat: "Oh, you're sure to do that, if you only walk long enough."

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Key Messages

1. Be clear are your terminology
2. Be clear on your goals
3. Disciplined subgroup search (DSS)
4. Always do subgroup ~~analysis~~ identification
5. One last idea

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1. Some Terminology

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1. Some Terminology

Precision medicine
Targeted therapy/therapeutics

vs

Personalized medicine

Targeted therapeutics = ***patients like*** **YOU**

Personalized medicine = **YOU**

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Targeted therapeutics = ***patients like* YOU**

Personalized medicine = **YOU**

1. Some Terminology

A *targeted therapeutic* allows the sponsor to make a regulatory approved claim of an expected treatment effect (efficacy or safety):

✓ Where the indicated patient population is itself selected by a biochemical, genetic or imaging biomarker.

✓ Where a subgroup of the indicated patient population (selected based on a clinical, biochemical, genetic, or imaging biomarker) is expected to have a *differential treatment effect*.

✓ Where individualized dosing (dose and/or duration) is based on a biomarker responsive to treatment.

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1. Some Terminology

Targeted therapeutics

means

Finding subgroups

Stephen J. Ruberg & Lei Shen (2015) Personalized Medicine: Four Perspectives of Tailored Medicine, Statistics in Biopharmaceutical Research, 7:3, 214-229.

2. Clarifying Goals

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2. Clarifying Goals

Targeted therapeutics

means

Finding subgroups

What's real versus what's spurious?

2. Clarifying Goals

Do you want to find a subgroup or not?

YES – Heterogeneity is my friend!

- I want to find a targeted therapeutic!

Clarifying Goals

Do you want to find a subgroup or not?

YES – Heterogeneity is my friend!

- I want to find a targeted therapeutic!

NO – Heterogeneity is my enemy!

- I want the treatment effect to be homogeneous across subgroups.

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3. Disciplined Subgroup Search (DSS)

Stephen J. Ruberg & Lei Shen (2015) Personalized Medicine: Four Perspectives of Tailored Medicine, Statistics in Biopharmaceutical Research, 7:3, 214-229.

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3. Disciplined Subgroup Search

Definition

Disciplined Subgroup Search (DSS) is

- a systematic approach to subgroup identification having
- several characteristics that are quite distinct
  - from those of a traditional subgroup analysis
  - or post hoc exploratory analysis of subgroups.

3. Disciplined Subgroup Search

DSS characteristics

1. **Prespecification**: the algorithm/methodology to be used for identifying subgroups, the list of biomarkers that form the covariate space to be searched, complexity of subgroup definitions (i.e., how many covariates are allowed to define the subgroup), as well as any other options/decisions that can be made in the analysis process.
   - In short, this is no different than prespecification of any important analysis in a Phase 3 trial that adheres to the ICH-E9 Guideline.

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3. Disciplined Subgroup Search

DSS characteristics

2. Adjusting for multiplicity: how statistical significance (i.e., *p*-values) of a subgroup finding will be adjusted for multiplicity. [Also consider Bayesian approaches.]

3. Bias correction: how estimates of treatment effect are corrected for bias due to the selection bias associated with searching multiple subgroups.

3. Disciplined Subgroup Search

DSS characteristics

4. Biomarker effects: allows for separating prognostic biomarker effects from predictive biomarker effects.

5. Interactions: allows for multiple biomarkers to be included in the definition of a subgroup.

6. Partition: allows for identification of a cut-off value for a continuous biomarker that separates smaller treatment effects from larger treatment effects.

[Features added to Ilya's table?]

4. Always Do Subgroup Identification (DSS)

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Subgroup Identification

"Always do subgroup *analysis*, but never believe them."

Attributed to Sir Richard Peto

Professor of Medical Statistics and Epidemiology

University of Oxford, England

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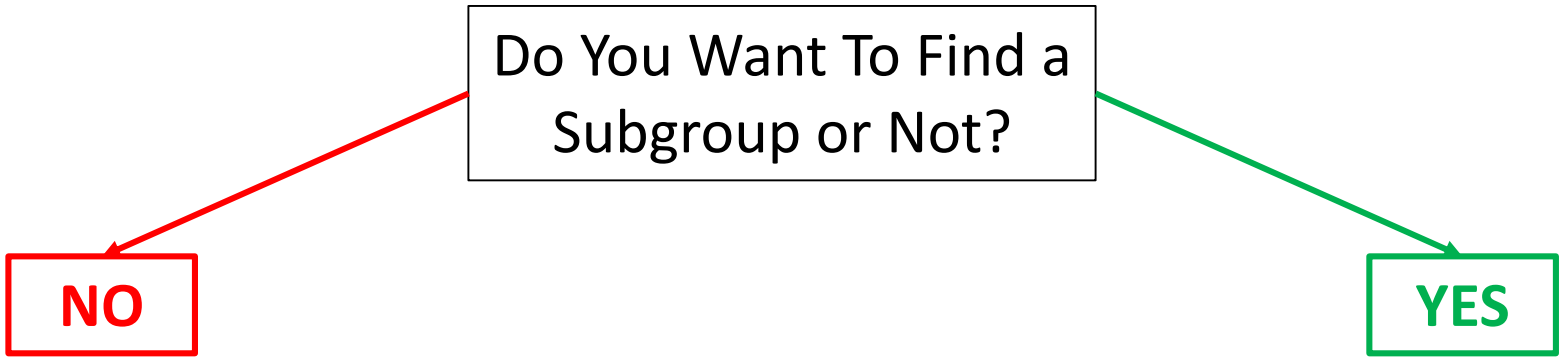
Subgroup Identification



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Subgroup Identification

Do You Want To Find a Subgroup or Not?

NO

"Routine" baseline factors

Playing "defense"

Avoid trying to explain away (unusual?) findings

Use DSS !!

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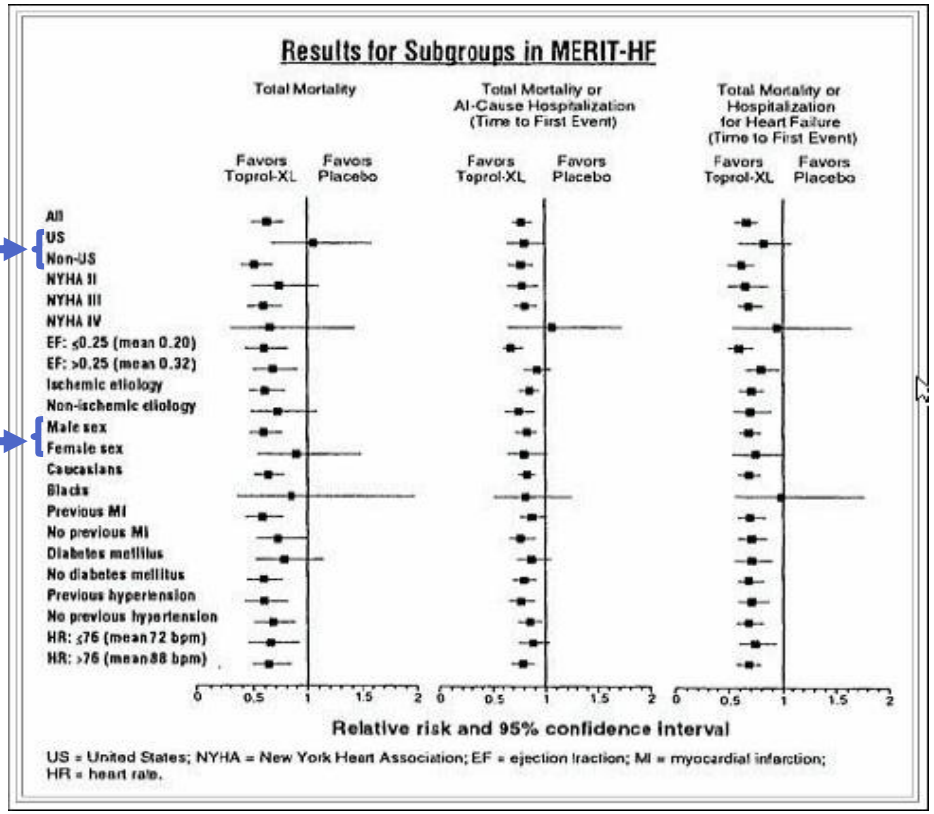

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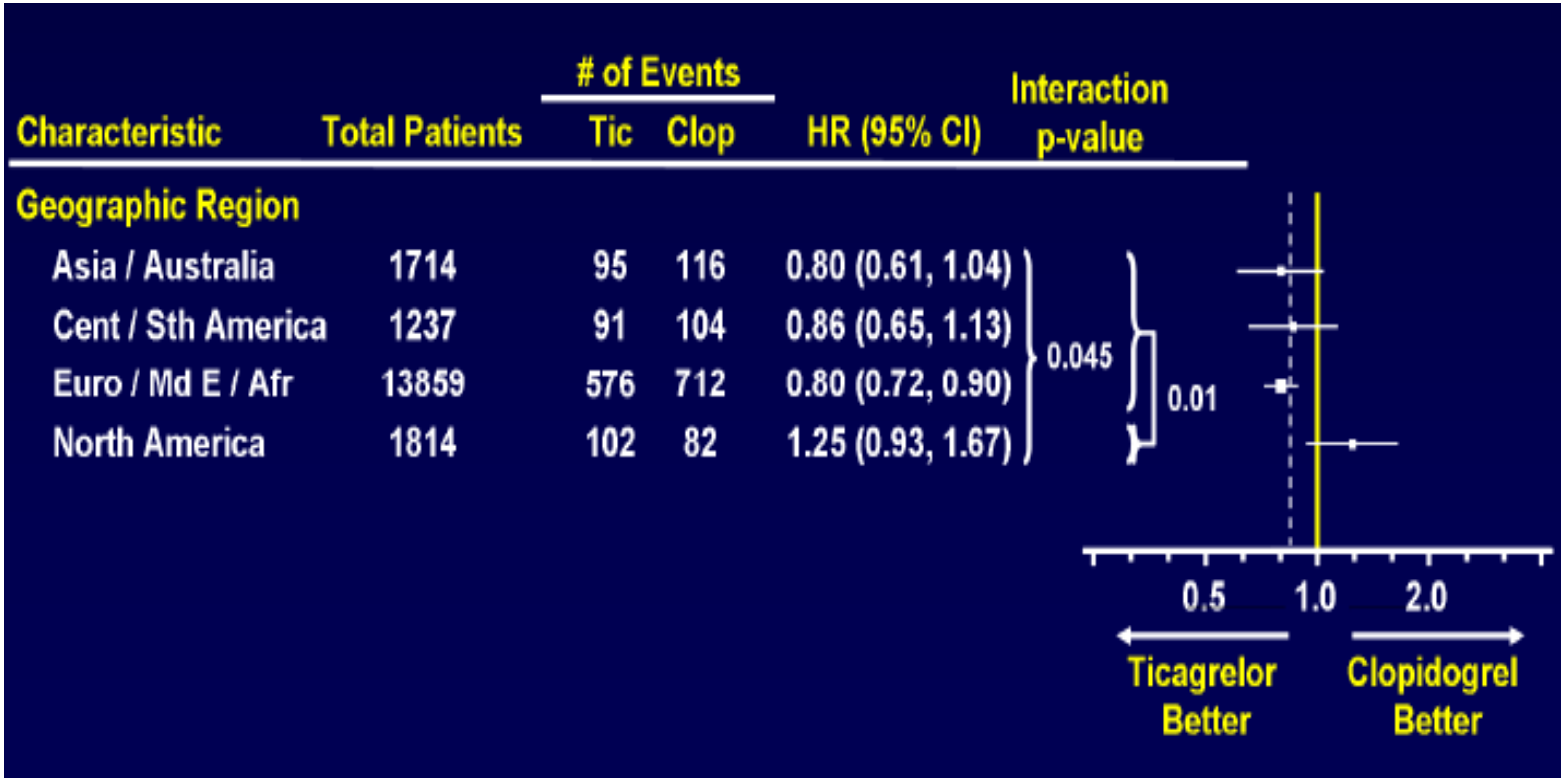
Subgroup Identification

"The figure … illustrates principal results for a wide variety of subgroup comparisons, including US vs. non-US populations (the latter of which was not pre-specified). The combined endpoints of all-cause mortality plus all-cause hospitalization and of mortality plus heart failure hospitalization showed consistent effects in the overall study population and the subgroups, including women and the US population. **However, in the US subgroup and women, overall mortality and cardiovascular mortality appeared less affected. Analyses of female and US patients were carried out because they each represented about 25% of the overall population.** Nonetheless, subgroup analyses can be difficult to interpret, and **it is not known whether these represent true differences or chance effects."**

From US Label for Toprol-XL

Subgroup Identification

Ticagrelor Example



Source: Sponsor presentation at CV and Renal Drugs Ad Comm Meeting July, 2010 CC-30

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Subgroup Identification

Always do subgroup identification !!!

What if DSS had been formally done?

- Often subgroups defined by baseline factors are described in the protocol (e.g. gender, race, baseline severity, etiology, etc.?
- What if the subgroup identification search methodology was pre-specified?
- What if *adjusted* p-values and effect estimates were calculated?
- *Would these surprising findings not be so surprising anymore?*

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Subgroup Identification

Do You Want To Find a Subgroup or Not?

YES

Many baseline factors, biomarkers, med Hx, etc.

Playing “offense”

Seeking to explain findings

Use DSS !!

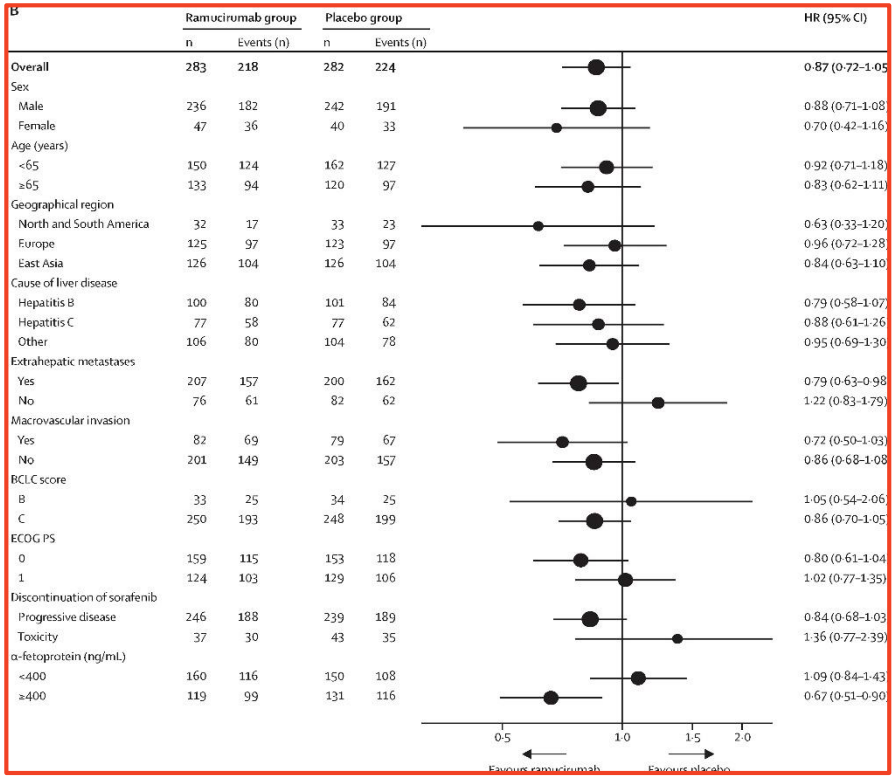
Bringing data to life.

Subgroup Identification

Ramucirumab vs Placebo in HCC (REACH)
Lancet Onc, 2015; 16, 859-870

Do You Want To Find a Subgroup or Not?

YES



B	Ramucirumab group		Placebo group		HR (95% CI)
	n	Events (n)	n	Events (n)	
Overall	283	218	282	224	0·87 (0·72–1·05)
Sex					
Male	236	182	242	191	0·88 (0·71–1·08)
Female	47	36	40	33	0·70 (0·42–1·16)
Age (years)					
<65	150	124	162	127	0·92 (0·71–1·18)
≥65	133	94	120	97	0·83 (0·62–1·11)
Geographical region					
North and South America	32	17	33	23	0·63 (0·33–1·20)
Europe	125	97	123	97	0·96 (0·72–1·28)
East Asia	126	104	126	104	0·84 (0·63–1·10)
Cause of liver disease					
Hepatitis B	100	80	101	84	0·79 (0·58–1·07)
Hepatitis C	77	58	77	62	0·88 (0·61–1·26)
Other	106	80	104	78	0·95 (0·69–1·30)
Extrahepatic metastases					
Yes	207	157	200	162	0·79 (0·63–0·98)
No	76	61	82	62	1·22 (0·83–1·79)
Macrovascular invasion					
Yes	82	69	79	67	0·72 (0·50–1·03)
No	201	149	203	157	0·86 (0·68–1·08)
BCLC score					
B	33	25	34	25	1·05 (0·54–2·06)
C	250	193	248	199	0·86 (0·70–1·05)
ECOG PS					
0	159	115	153	118	0·80 (0·61–1·04)
1	124	103	129	106	1·02 (0·77–1·35)
Discontinuation of sorafenib					
Progressive disease	246	188	239	189	0·84 (0·68–1·03)
Toxicity	37	30	43	35	1·36 (0·77–2·39)
α-fetoprotein (ng/mL)					
<400	160	116	150	108	1·09 (0·84–1·43)
≥400	119	99	131	116	0·67 (0·51–0·90)

Many baseline factors, biomarkers, med Hx, etc.

Playing "offense"

Seeking to explain findings

Use DSS !!

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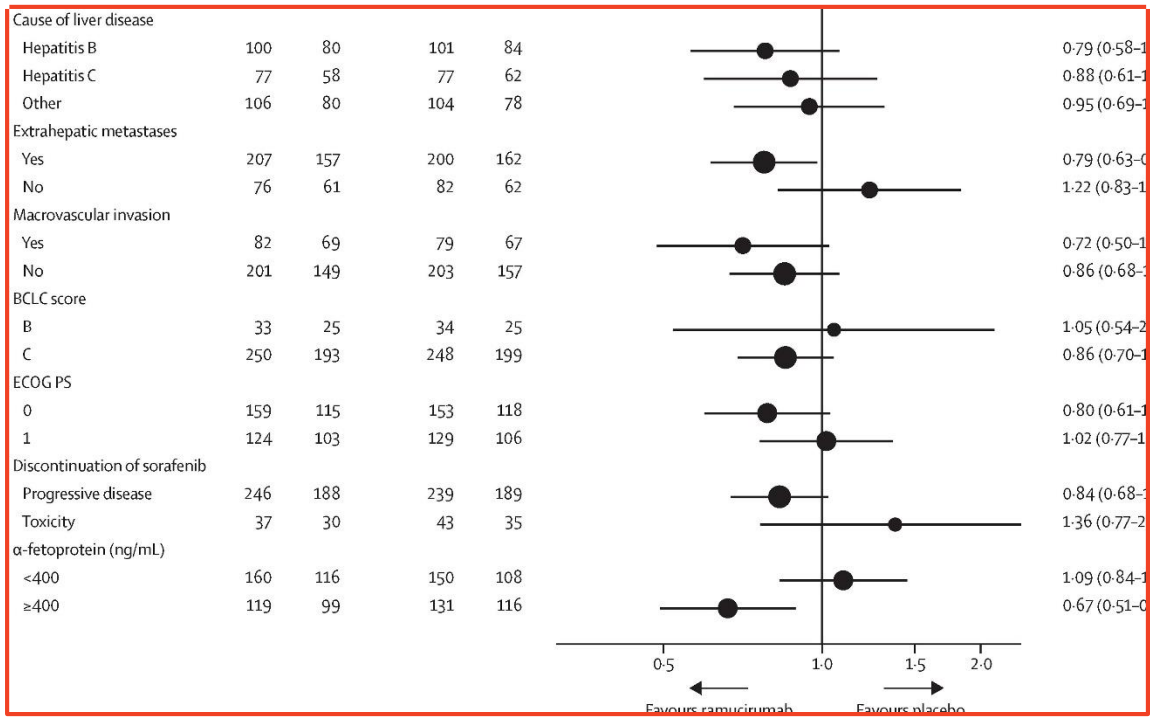

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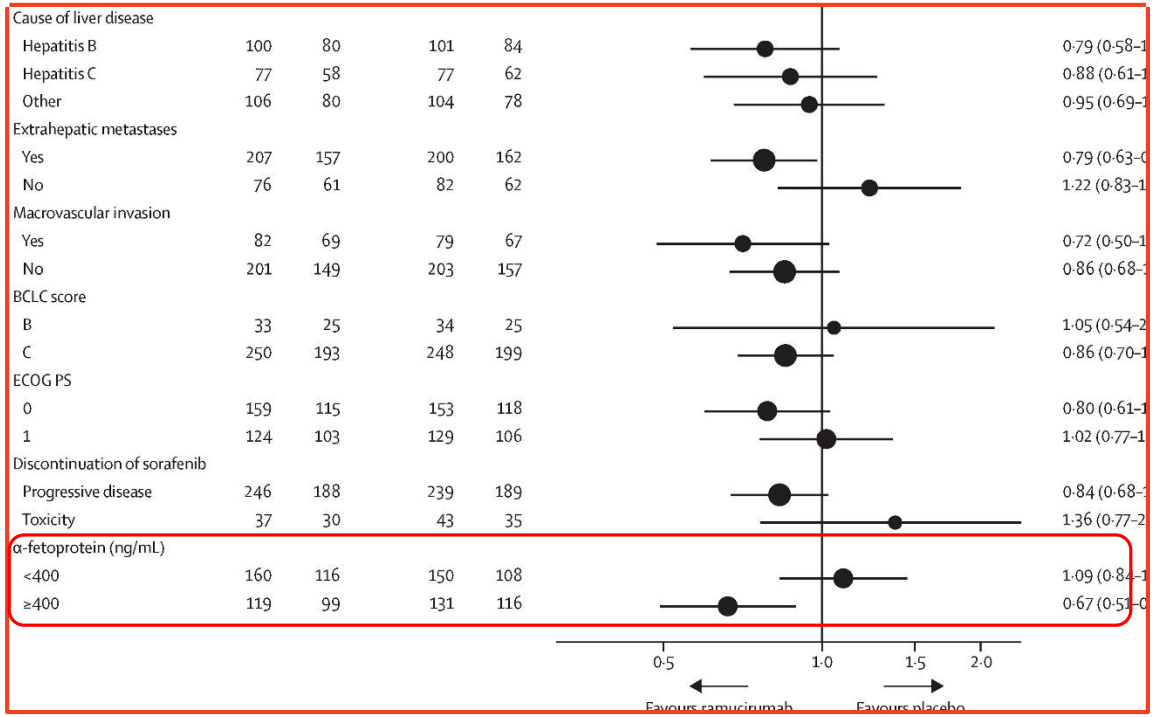

Many baseline factors, biomarkers, med Hx, etc.

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Subgroup Identification

Ramucirumab vs Placebo in HCC with elevated AFP (REACH-2)
Lancet Onc, 2019; 20, 282-296

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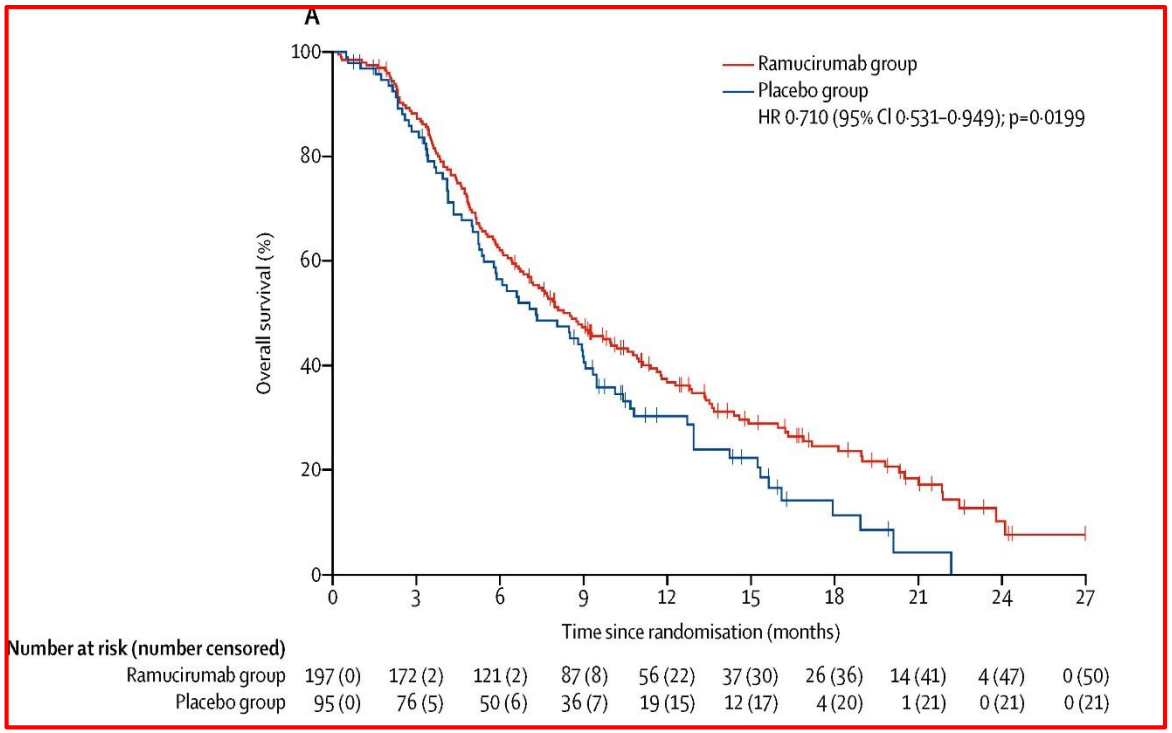

Many baseline factors, biomarkers, med Hx, etc.

Playing "offense"

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Use DSS !!

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Subgroup Identification

Always do subgroup identification !!!

What if DSS had been formally done in REACH?

- What if the AFP subgroup was pre-specified along with other subgroups?
- What if the subgroup identification search methodology was pre-specified?
- What if *adjusted* p-values and effect estimates were calculated?
- *What if they were still significant and meaningful?*

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Subgroup Identification

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What if DSS had been formally done in REACH?

- What if the AFP subgroup was pre-specified along with other subgroups?
- What if the subgroup identification search methodology was pre-specified?
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- What if they were still significant and meaningful?

But … DSS is hard !!!!!

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Subgroup Identification

The $1,000,000,000 [read billion] question …

Could ramucirumab have been approved in the targeted subgroup based on REACH in 2015 using DSS instead of

- Spending 3 years, and
- Many, many millions of dollars, and
- Tens of thousands of patients not having access to an effective medication?

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Subgroup Identification

The $1,000,000,000 [read billion] question …

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- Spending 3 years, and
- Many, many millions of dollars, and
- Tens of thousands of patients not having access to an effective medication?

Is DSS a billion dollars hard?!?!?!?

Subgroup Identification

"Always do subgroup *identification using DSS* so the results are more believable."

Steve Ruberg

Your Run-of-the-Mill Statistician

5. One More Idea

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One More Idea

Suppose there are **100** potential predictive biomarkers that could be important for a new treatment.

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Observed p-value = **0.0001** for one biomarker

- Bonferroni adjusted p-value $\leq$ **100** * **0.0001** = **0.01**

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One More Idea

Suppose there are **100** potential predictive biomarkers that could be important for a new treatment.

Observed p-value = **0.0001** for one biomarker

- Bonferroni adjusted p-value $\leq$ **100** * **0.0001** = **0.01**

EUREKA! We have discovered a novel biomarker-defined subgroup.

One More Idea

ARE YOU SURE?

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One More Idea

ARE YOU SURE?

Suppose further

pr(success … finding a biomarker)

= pr(at least one H_0 is false) = **0.20**

Prior on H_0 is true (none are predictive) = 0.80

One More Idea

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Uniform prior per biomarker = **0.20**/**100** = **0.002**

One More Idea

Let p_0 = prior probability that H_0 is false (e.g. the biomarker is predictive)

Let p = observed p-value for test statistics for H_0

Bayes factor* $\mathbf{[-e \times p \times \ln(p)]^{-1}}$ can be used to give an upper bound on the posterior probability that H_0 is false

*Sellke et al (2001) Calibration of p Values for Testing Precise Null Hypotheses. The American Statistician, February 2001, Vol. 55, No. 1, pp 62-71.

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Posterior probability** for H_0 being false (p_1) is (upper bound)

$$p_1 \leq \{1 + [(1-p_0)/p_0] \times [-e \times p \times \ln(p)]\}^{-1}$$

Posterior ← Prior ← New Data

*Sellke et al (2001) Calibration of p Values for Testing Precise Null Hypotheses. The American Statistician, February 2001, Vol. 55, No. 1, pp 62-71.

**If $p < 1/e = .368$

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One More Idea

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Prior on H_0 is true (none are predictive) = 0.80

Uniform prior per biomarker = **0.20**/**100** = **0.002**

Bayesian posterior pr(H_0 is false) ≤ 0.44.

Berger J.O., Wang X., Shen L. (2014). A Bayesian approach to subgroup identification. *J Biopharm Stat,* 24(1), 110-29.

AnalytixThinking.blog

Subgroup Identification

"Always use *Bayesian thinking* when doing subgroup identification so you can quantify how believable the results are."

Steve Ruberg

Your Run-of-the-Mill Bayesian Statistician

Conclusion

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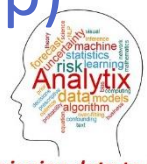
Conclusion

Subgroup identification is the HOLY GRAIL.

Not surprisingly, that makes it **the hardest problem there is**.

- Size of the subgroup (10, 20, … 50%)
- Differential effect in the subgroup (5, 15, 25%)
- No. of biomarkers (3, 10, 100, 1000, … 10^6)
- No. of biomarkers defining the subgroup (1,2,3, …)
- Nature of biomarker effect (step or smooth curve)
- Size of the clinical trial (100, 250, 500, 1000/group)



Conclusion

ALWAYS do subgroup identification …

To find or not to find …

Disciplined Subgroup Search

(replication and biological plausibility are very important)

Conclusion

ALWAYS do subgroup identification …

To find or not to find …

Disciplined Subgroup Search

When I see a **significant subgroup finding**, I always ask …

“I wonder what their prior was?”

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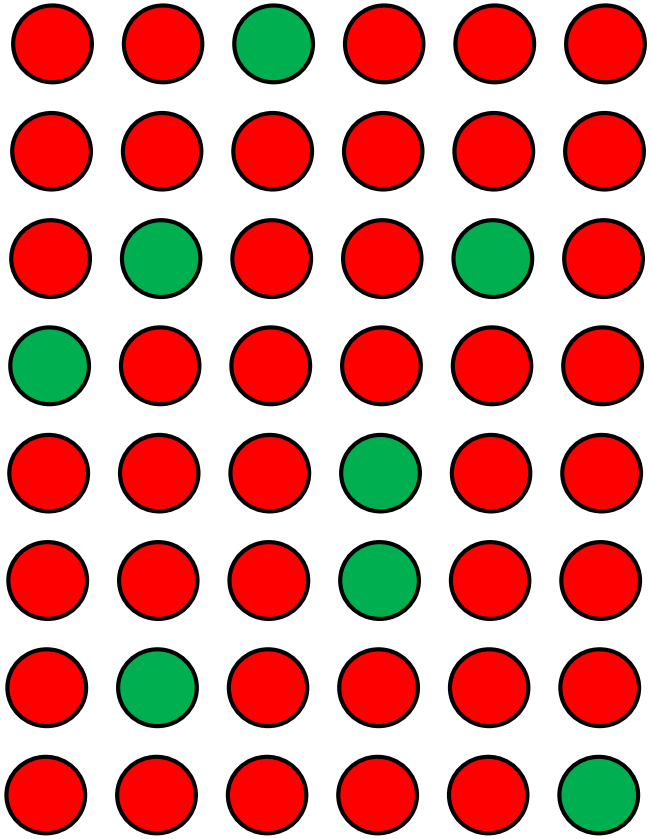
THANK YOU

X > a



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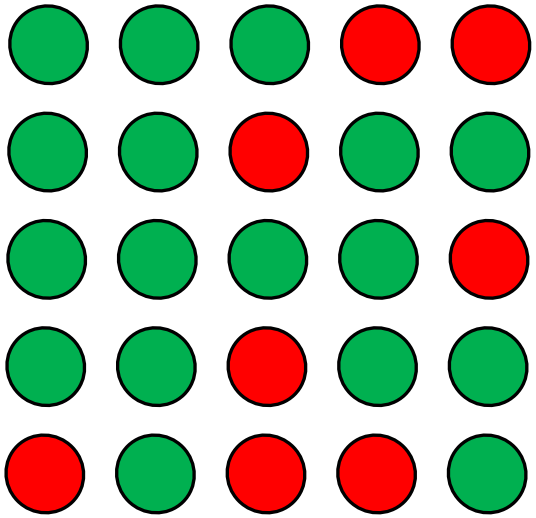

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