Use of Subgroups to "Rescue" a Trial or Improve Benefit-Risk

Martin King, Ph.D.

Director, Statistics

Global Pharmaceutical R&D, Abbott

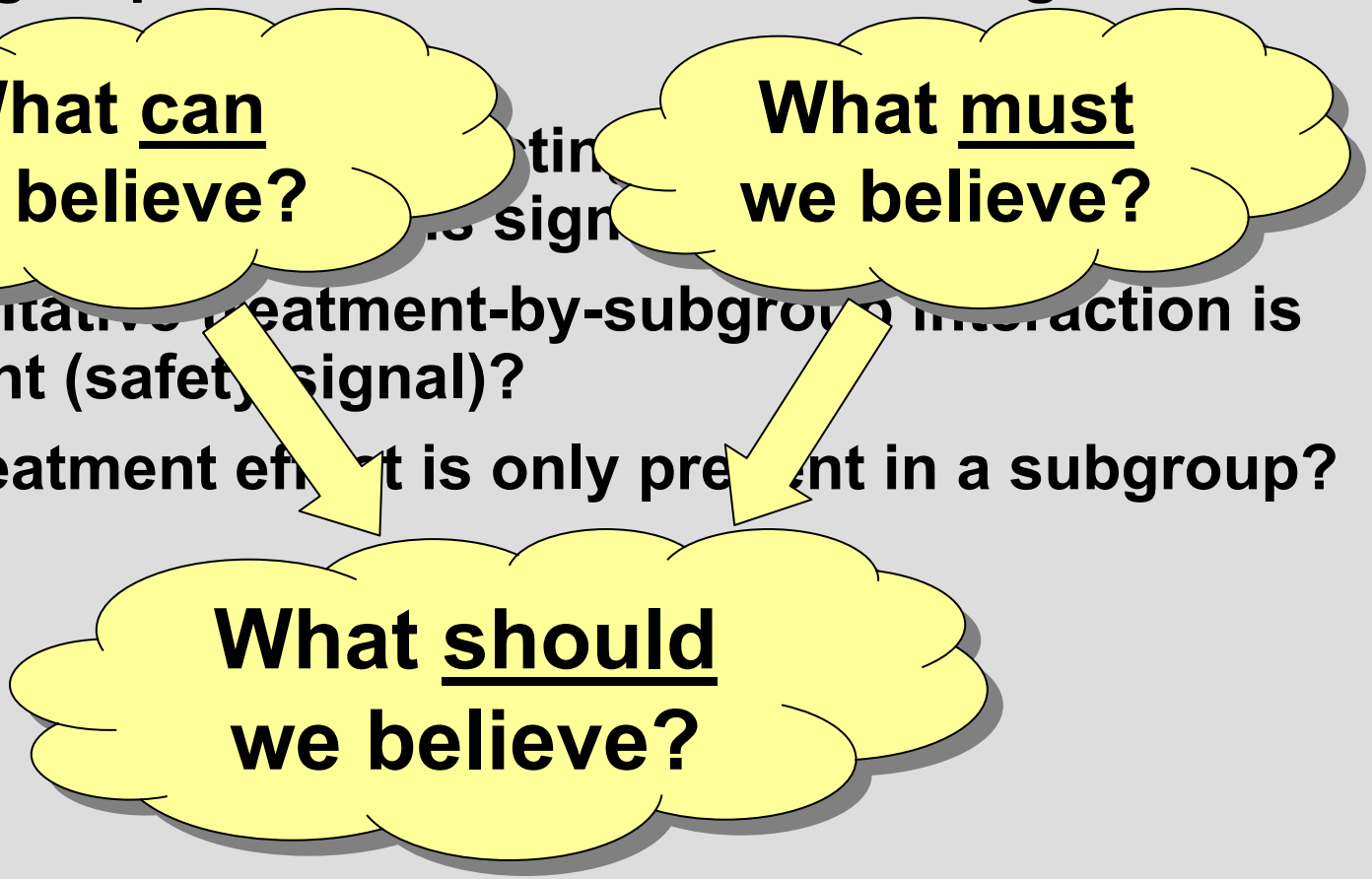
Abbott Park, IL USA

Disclaimer

- The opinions in this presentation are those of the author and not necessarily those of Abbott

Questions for Consideration

- Under what circumstances should we consider approval for a subgroup if the overall result is non-significant?
- S… tin… w… …s sign…
  - a qualitative treatment-by-subgroup interaction is present (safety signal)?
  - the treatment effect is only present in a subgroup?



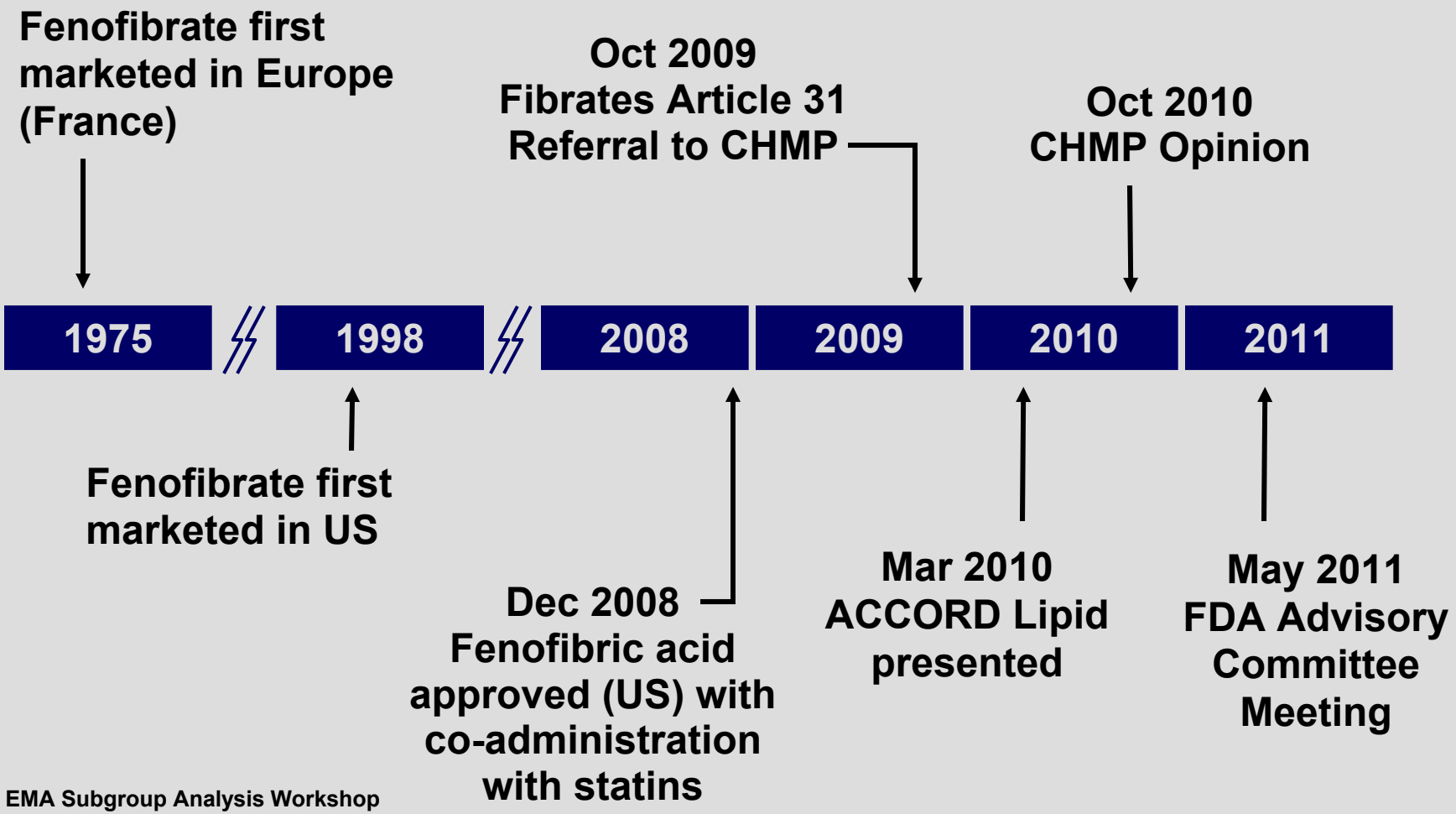
Fibrate Drug Class – Background

- Bezafibrate
- Ciprofibrate
- Clofibrate
- Fenofibrate
- Fenofibric acid
- Gemfibrozil

} Share same active moiety

- Fibrates reduce triglycerides (TG) and increase HDL cholesterol (HDL-C)
- Fibrates approved in the EU and US as monotherapy for isolated severe hypertriglyceridaemia

Fenofibrate/Fenofibric Acid History



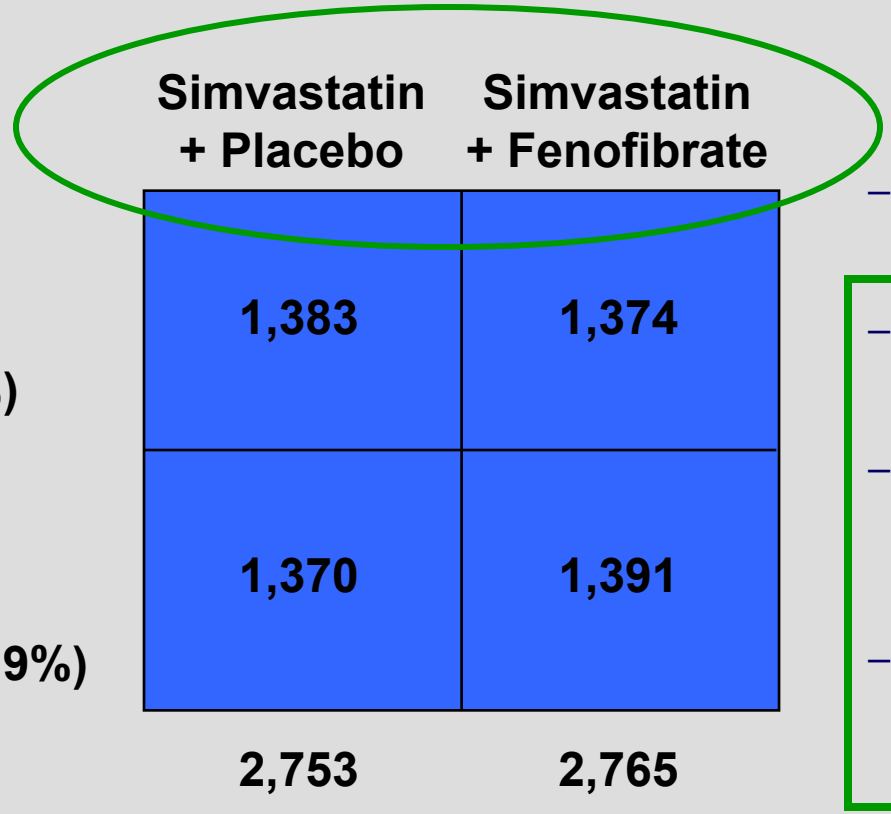
Trilipix (Fenofibric Acid) Approved Coadministration Indication

- **Trilipix was approved by FDA 15 Dec 2008 with the following coadministration indication:**
  - An adjunct to diet in combination with a statin to reduce TG and increase HDL-C in **patients with mixed dyslipidemia** and CHD or a CHD risk equivalent who are **on optimal statin therapy** to achieve their LDL-C goal

Suggests: Combination therapy can be considered for patients already receiving statins if they still have dyslipidemia (presumably elevated TG or low HDL-C)

Fenofibric Acid Labeling and Treatment Guidelines Suggest Combination Treatment for Residual High TG or Low HDL-C

ACCORD Lipid Study Design



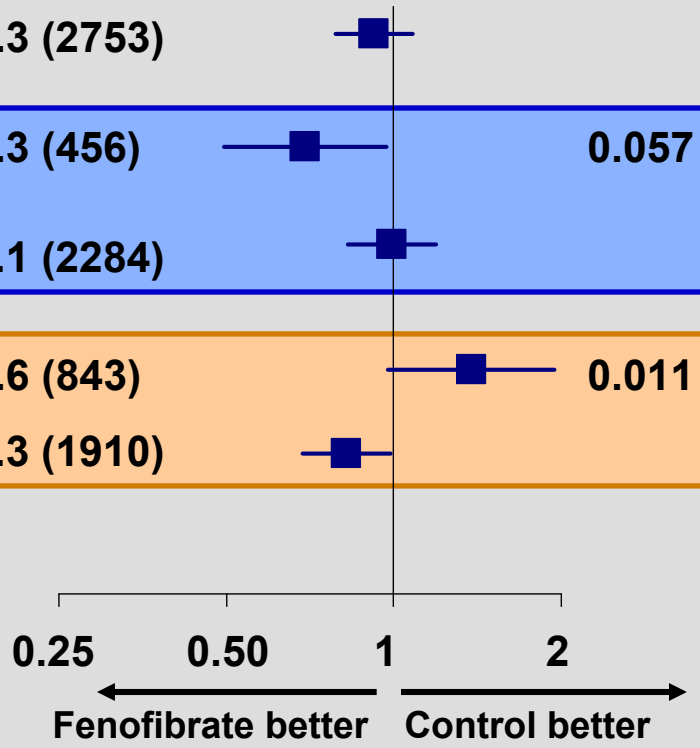
Select Entry Criteria

- LDL-C 60 - 180 not receiving lipid medications
- HDL-C < 55 (female or black) or < 50 (others)
- TG < 750 on no meds or < 400 on meds (no minimum TG threshold)
- Patients allowed but not required to be receiving a statin at study entry

http://www.accordtrial.org/public/slides.cfm

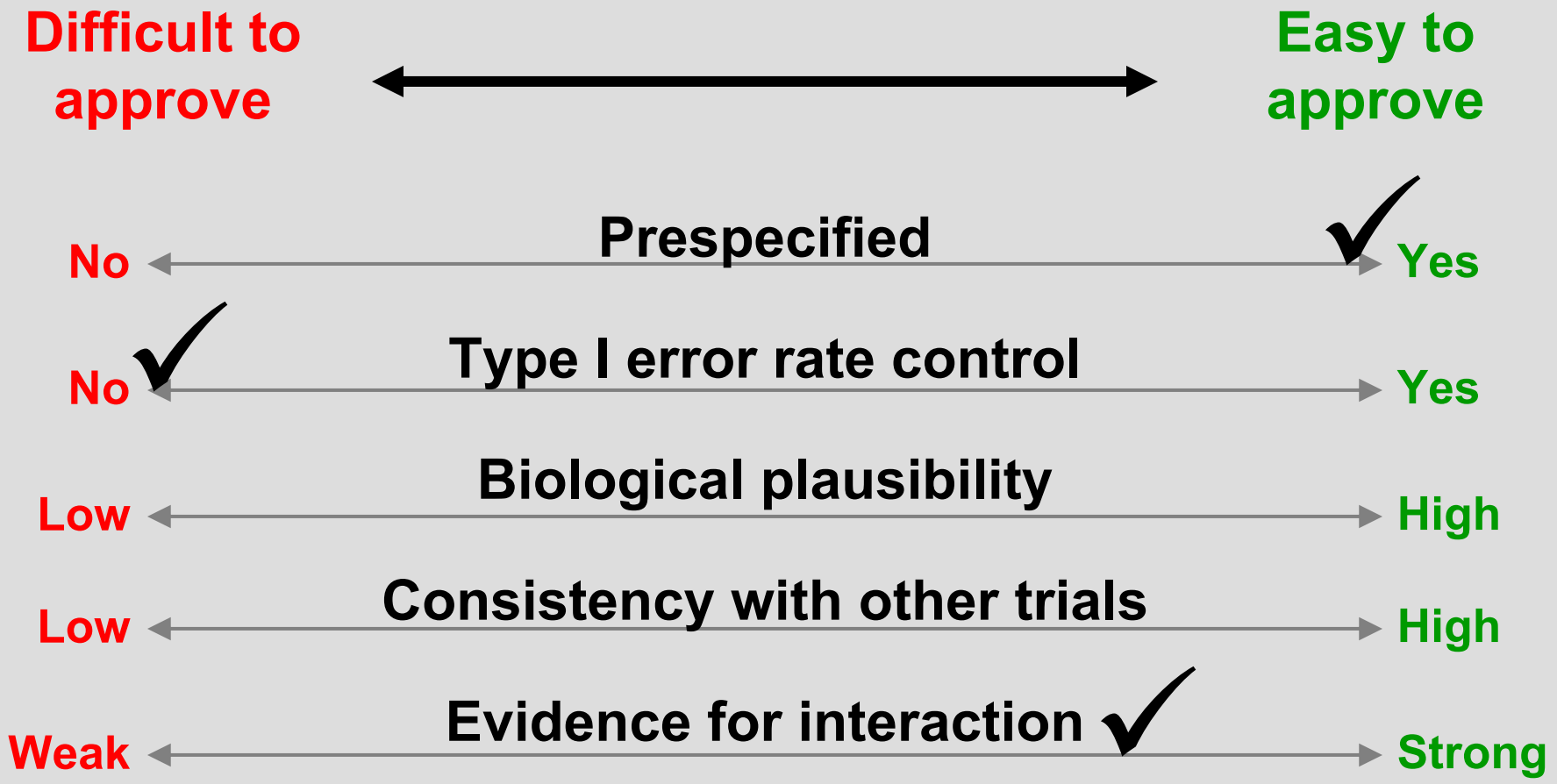
ACCORD Lipid Key Subgroup Results

	Fenofibrate-simvastatin	Simvastatin monotherapy	Hazard ratio (95% CI)	Interaction p-value	Within-group p value
	% with events (N)				
Overall	10.5 (2765)	11.3 (2753)			0.324
Dyslipidemic Patients*	12.4 (485)	17.3 (456)		0.057	0.032
All Others	10.1 (2264)	10.1 (2284)			0.935
Women	9.0 (851)	6.6 (843)		0.011	0.069
Men	11.2 (1914)	13.3 (1910)			0.037

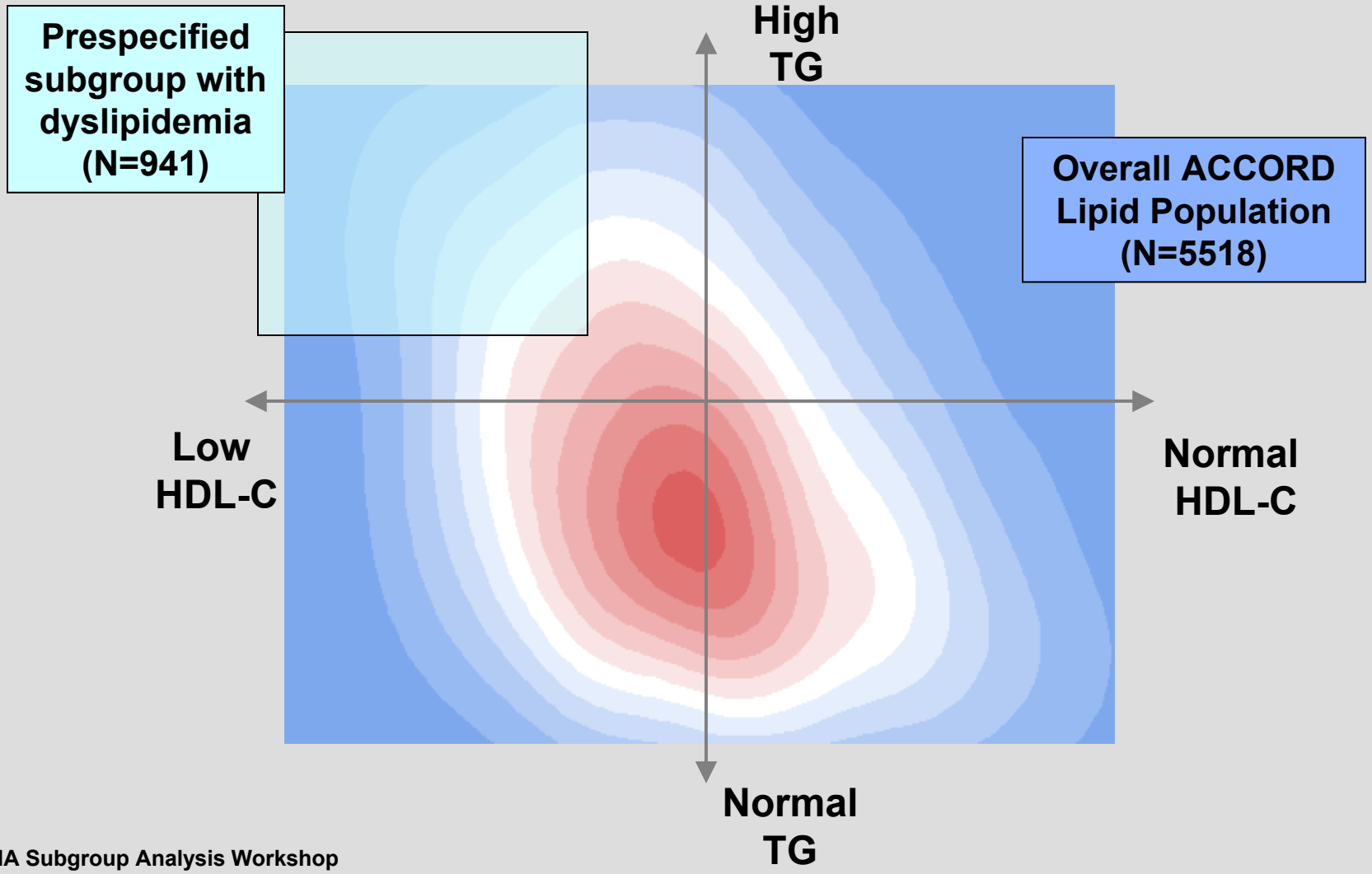


* Prespecified Subgroup:
Baseline TG ≥ 204 mg/dL and
HDL-C ≤ 34 mg/dL

When should we consider approval for a subgroup if the overall result is nonsignificant?

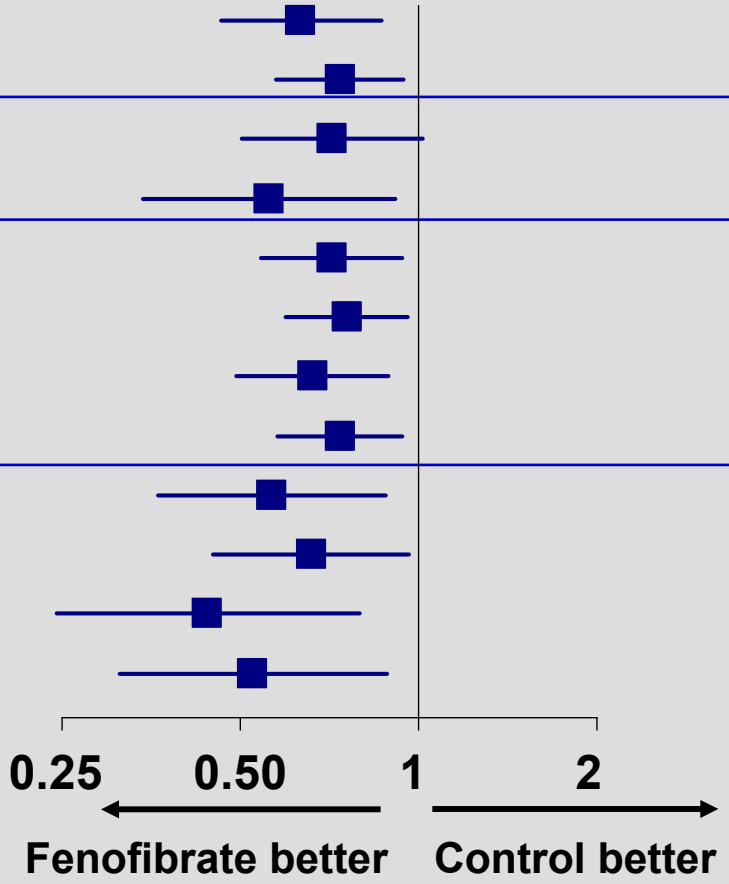


Prespecified Subgroup with Dyslipidemia in ACCORD Lipid

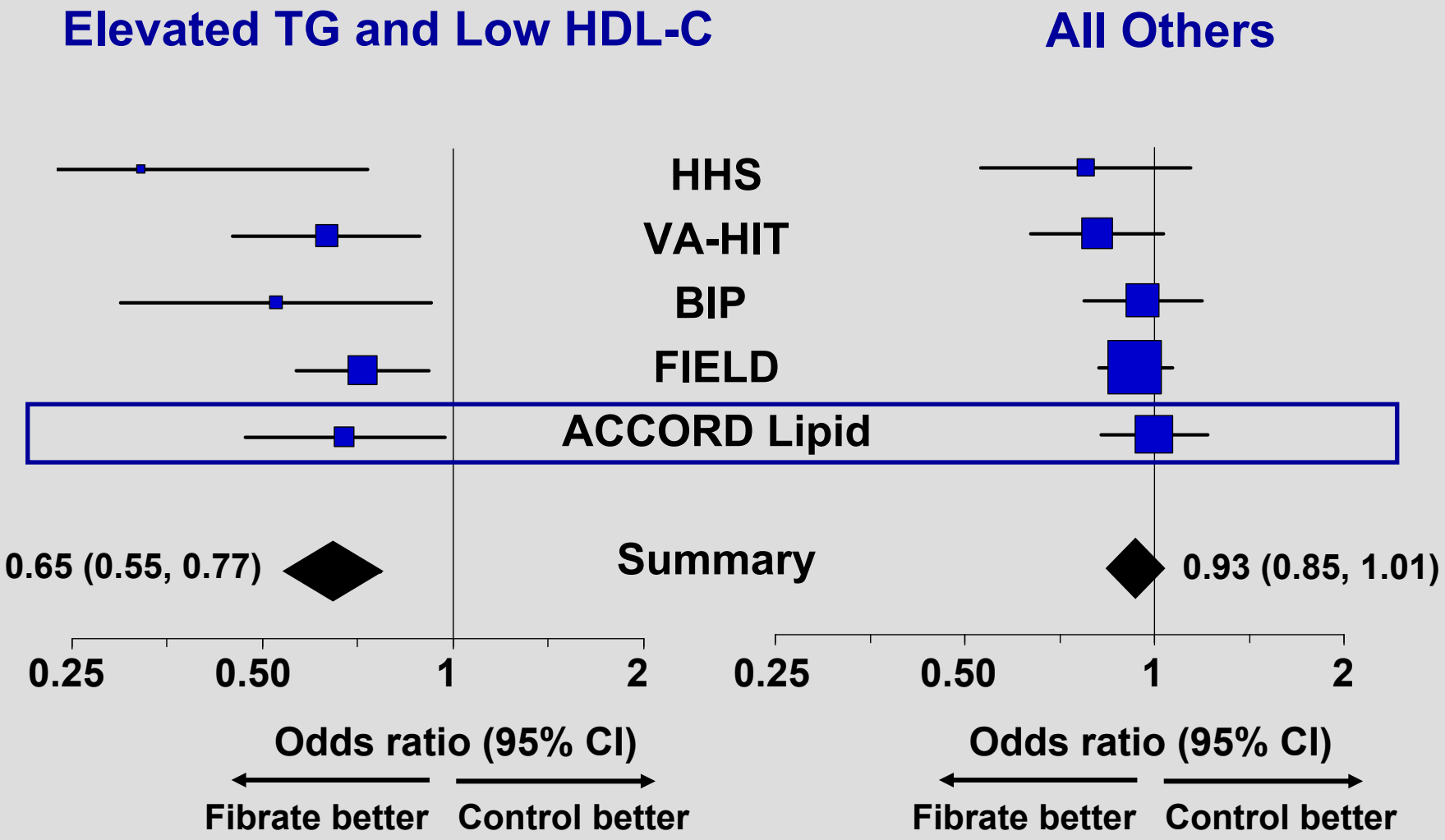


CV Risk Reduction in Patients Receiving a Statin at Baseline in ACCORD Lipid

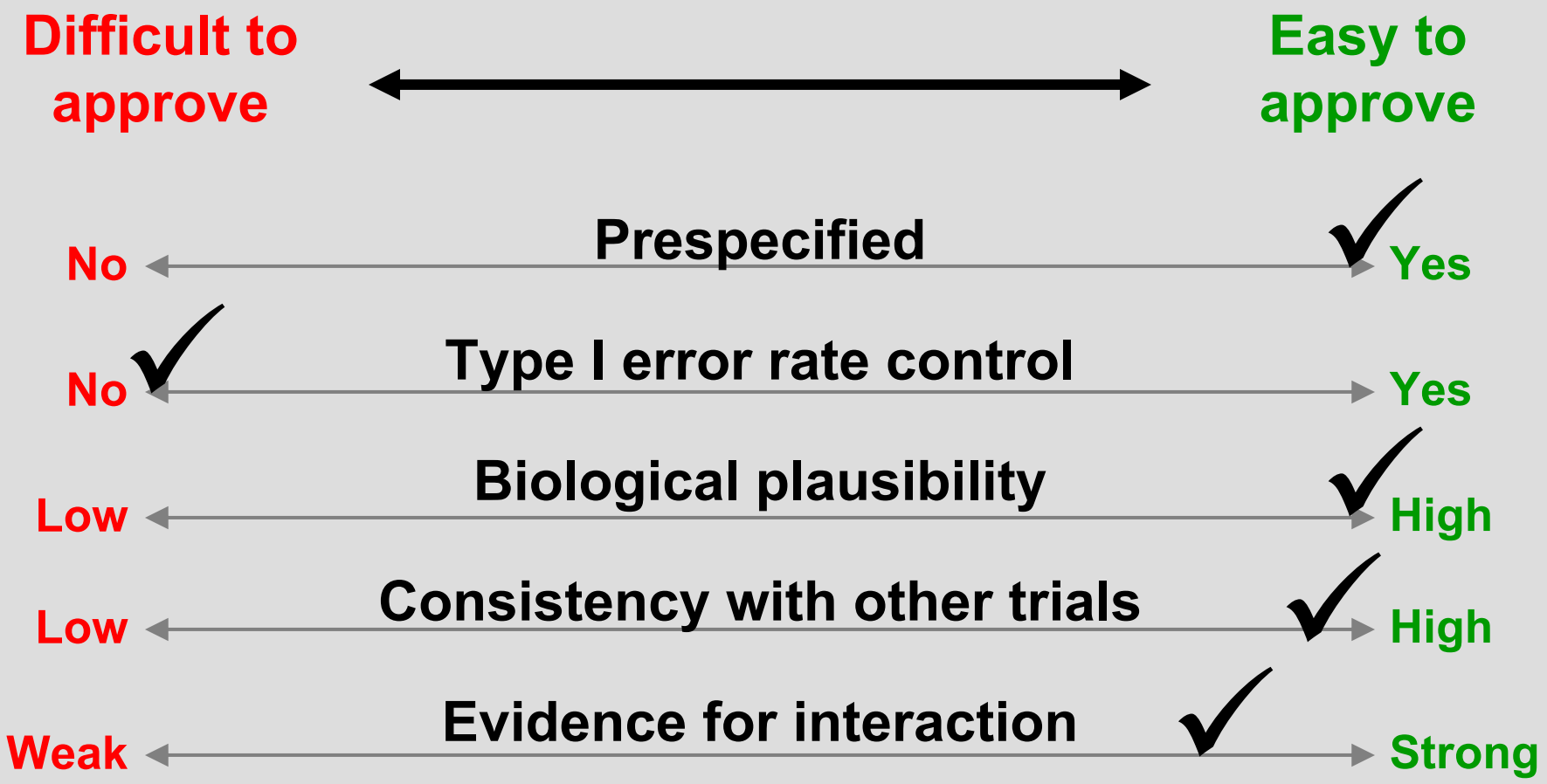
Baseline lipid values TG		HDL-C	Hazard ratio (95% CI)
-		≤ 34	
-		< 40	
≥ 200		-	
≥ 250		-	
≥ 200	or	≤ 34	
≥ 200	or	< 40	
≥ 250	or	≤ 34	
≥ 250	or	< 40	
≥ 200	and	≤ 34	
≥ 200	and	< 40	
≥ 250	and	≤ 34	
≥ 250	and	< 40	



ACCORD Lipid Consistent with Earlier Fibrate CV Outcomes Trials



Scorecard – ACCORD Lipid results in Subgroup with Dyslipidemia

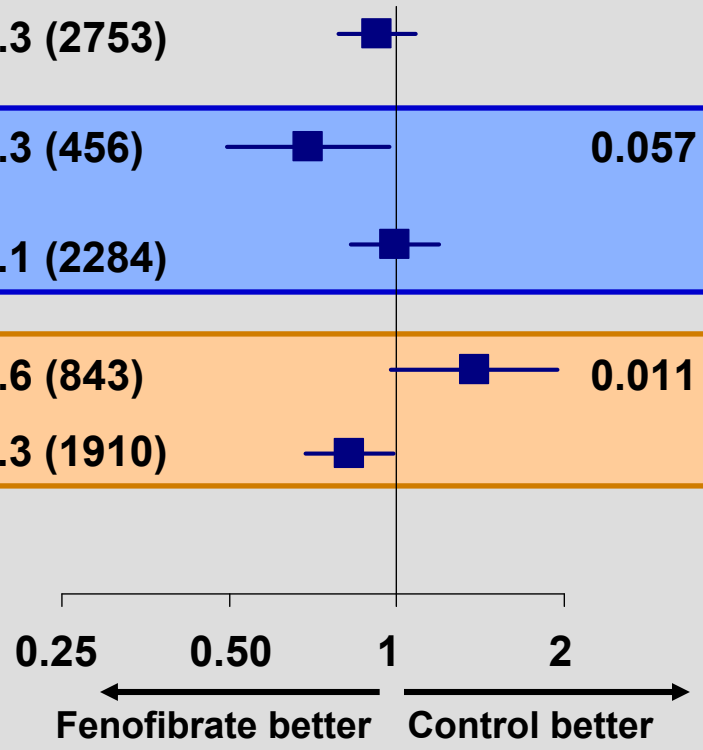


Regulatory Actions

- CHMP, October 2010
  - Majority vote that fenofibrate "can also be used together with a statin in some circumstances when a statin on its own has not been enough to completely control blood lipid levels"
- US FDA Advisory Committee, May 2011
  - Vote of 9–4 to retain coadministration indication of fenofibric acid
  - Vote of 13–0 in favor of an additional trial to confirm benefit

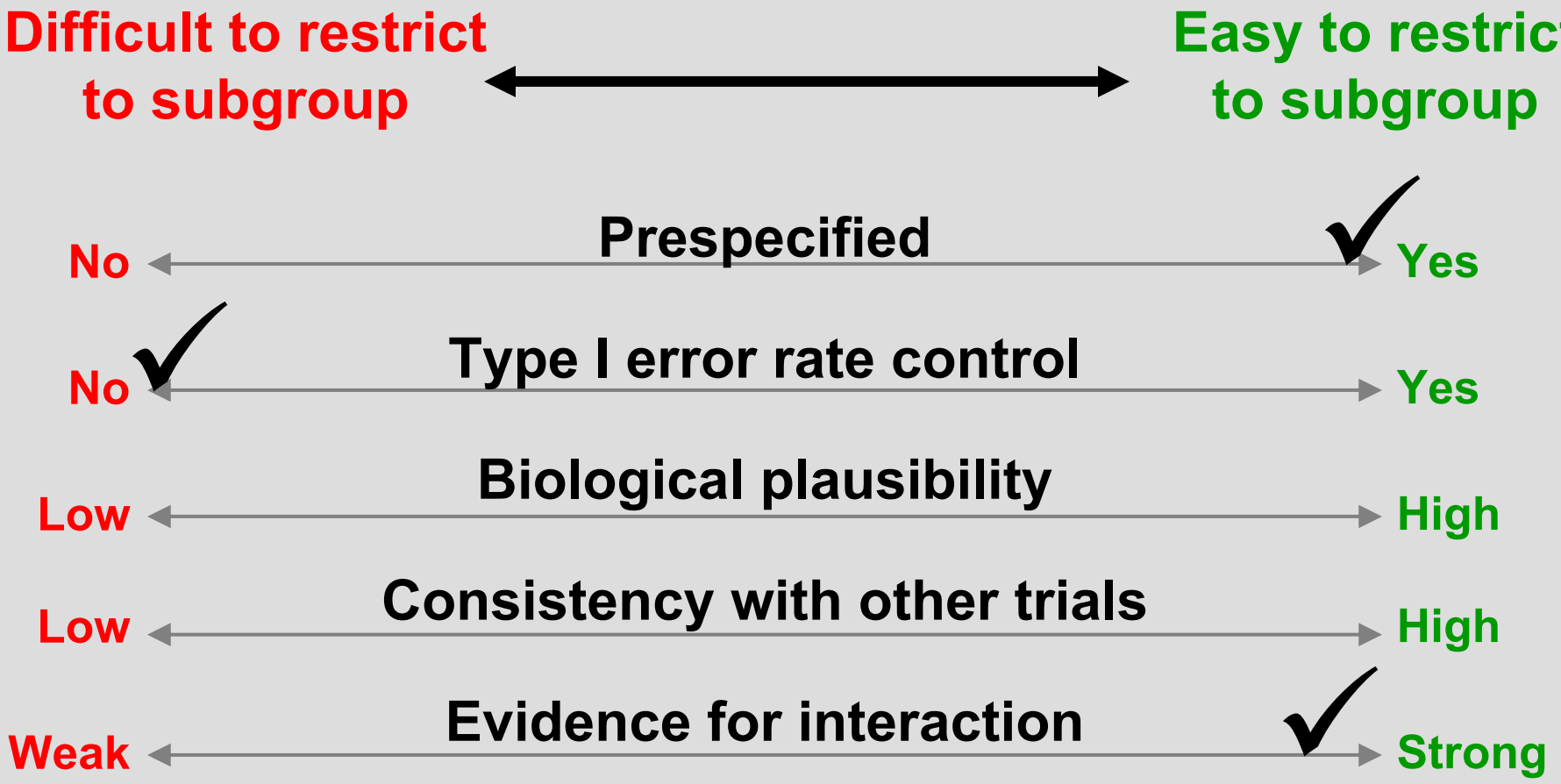
ACCORD Lipid Key Subgroup Results

	Fenofibrate-simvastatin % with events (N)	Simvastatin monotherapy % with events (N)	Hazard ratio (95% CI)	Interaction p-value	Within-group p value
Overall	10.5 (2765)	11.3 (2753)			0.324
Dyslipidemic Patients*	12.4 (485)	17.3 (456)		0.057	0.032
All Others	10.1 (2264)	10.1 (2284)			0.935
Women	9.0 (851)	6.6 (843)		0.011	0.069
Men	11.2 (1914)	13.3 (1910)			0.037



* Prespecified Subgroup: Baseline TG ≥ 204 mg/dL and HDL-C ≤ 34 mg/dL

When should we restrict approval to a subgroup?



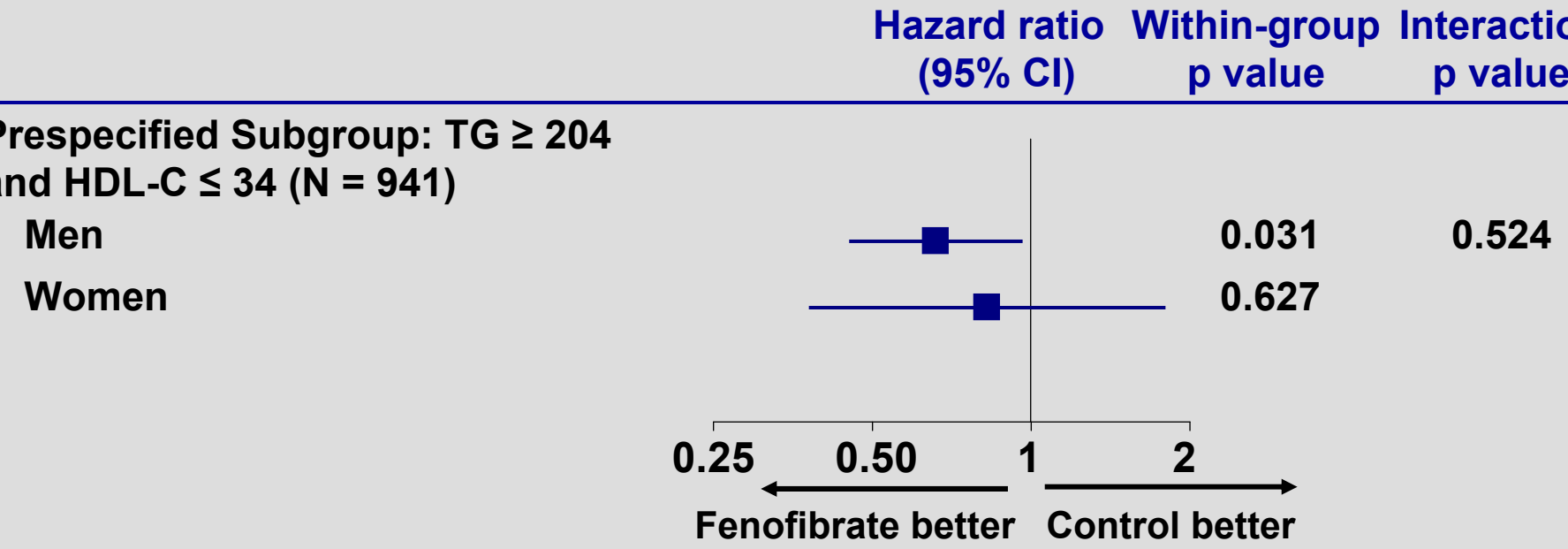
Biological plausibility of a treatment-by-gender interaction

- Several issues evaluated:
  - Outcomes by gender in subgroup with dyslipidemia
  - Potential explanations
    - Baseline imbalances
    - Lipid changes
    - Other laboratory changes
    - Pharmacokinetic interactions

Potential Explanations for Treatment-by-Gender Interaction in ACCORD Lipid

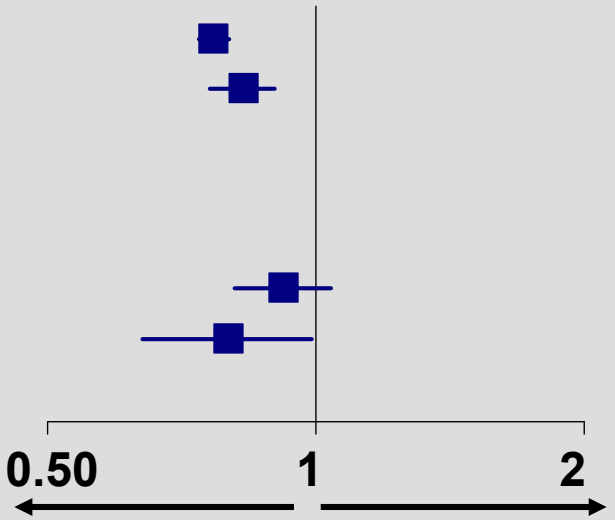
Factor	Finding
Baseline imbalances	No meaningful imbalances; multivariable analyses did not alter findings
Lipid changes	Lipid changes in women similar to or better than those in men
Other laboratory changes	No differential gender effects
Pharmacokinetic interactions	No gender effects on fibrate-statin interactions

No Treatment-by-Gender Interaction in Prespecified Subgroup with Dyslipidemia



No Qualitative Treatment-by-Gender Interaction in Statin or Fenofibrate Monotherapy Trials

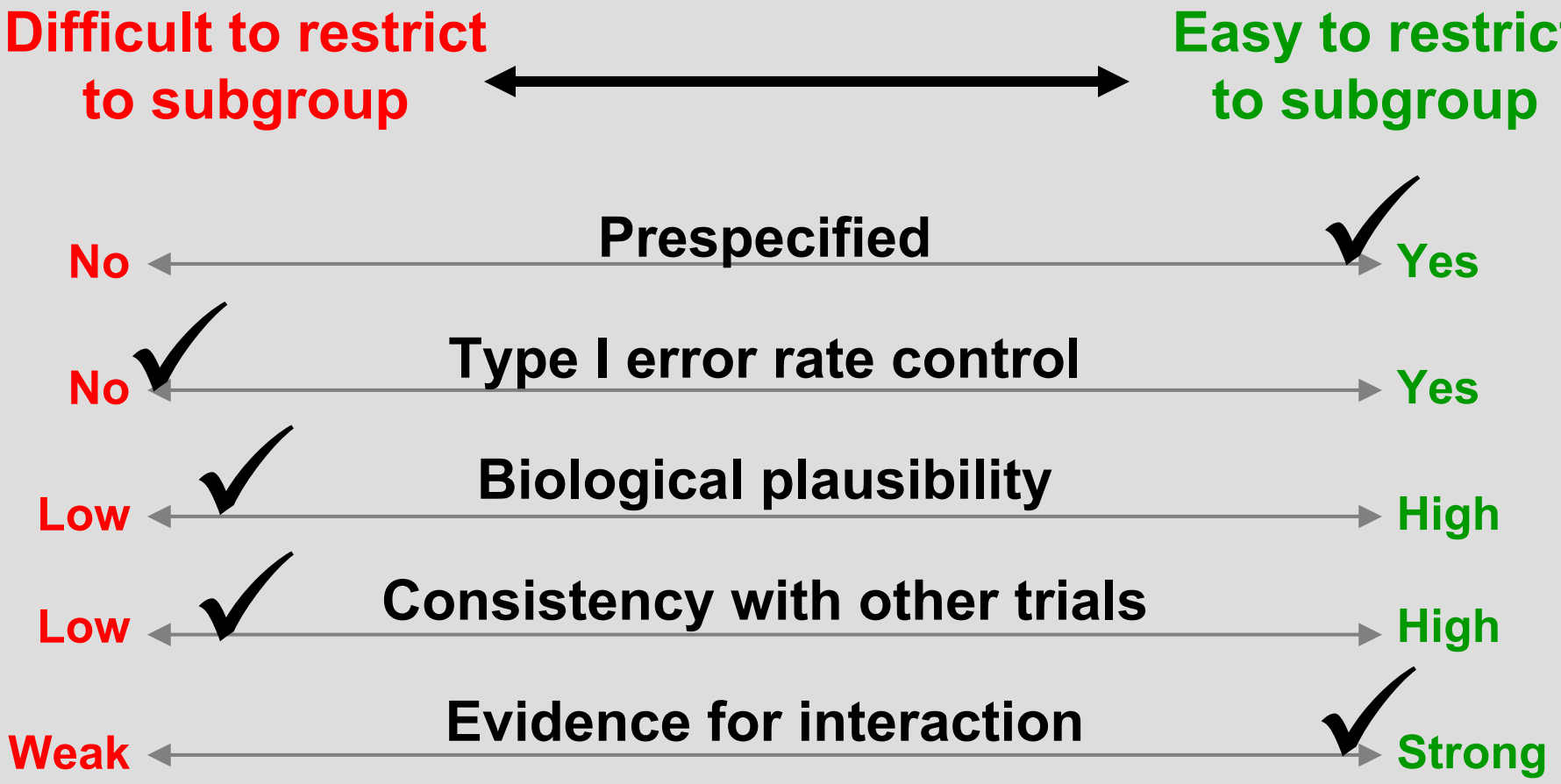
	Relative Risk* or Hazard Ratio (95% CI)	Interaction p-value
Cholesterol Treatment Trialists' Collaboration (statins)		
Men		0.04
Women		
FIELD Trial (fenofibrate)		
Men		ns
Women		



* For CTT: relative risk per 1 mmol/L reduction in LDL-C

Lancet. 2010;376:1670-1681.
*Diabetes Care. 2009;*32:493-498.

Scorecard – ACCORD Lipid Results by Gender



Regulatory Actions

- In product labeling, a description of the ACCORD Lipid trial and results was added, including description of the results by gender

Summary

- Approving subgroups (efficacy)
  - If not part of a prespecified plan with strong FWER
    biolo
    ra
- Restricting to su roups (safety)
  - If statistical evi nce strong, d t conclude type I error without thorough investi ion of biological plausibilit

What can we believe?

What must we believe?

What should we believe?