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Ongoing Long Term Studies

Rosiglitazone in Ongoing CV Outcomes Studies

ACCORD (NHLBI-sponsored):

- 10,251 patients T2DM; ~2000 RSG-treated
- Primary Endpoint: MACE (non-fatal MI, non-fatal stroke, CV death)

BARI – 2D (NHLBI-sponsored)

- 2300 patients T2DM with CAD; ~700 RSG-treated
- Primary Endpoint: All cause mortality

VADT (VA-sponsored)

- 1792 subjects T2DM; ~1100 RSG-treated
- Primary Endpoints: Composite of MI, CV death, CVA, CHF, PCI, amputation, limb ischemia

GSK-Sponsored Studies

APPROACH

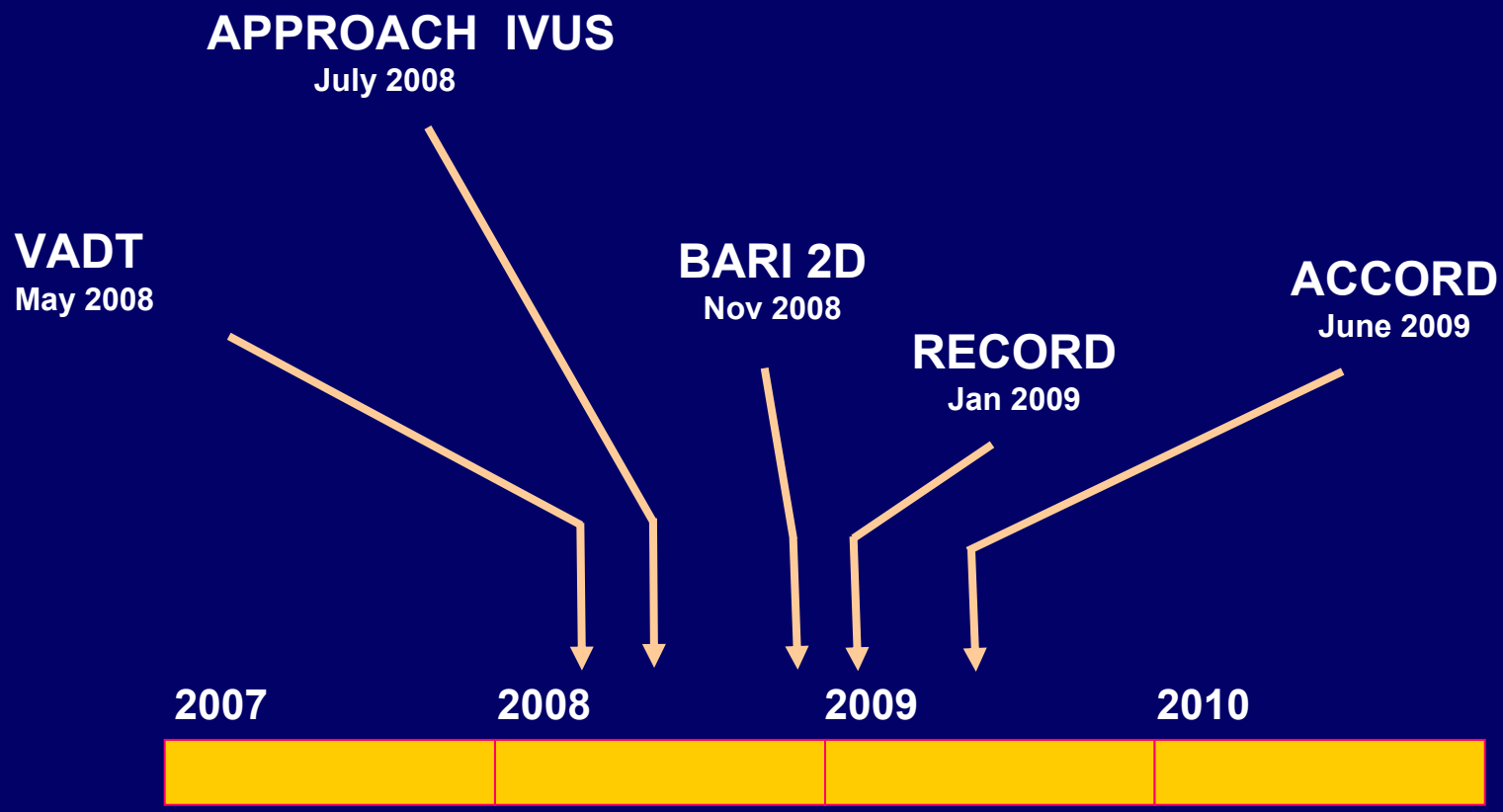
- 672 patients T2DM; 336 RSG-treated
- Primary Endpoints: Change in atheroma volume by quantitative IVUS

RECORD

- 4400 patients T2DM; ~2200 RSG-treated
- Study continues unaltered

CV Outcome Studies – Timelines*

Approximately an additional 22,000 patient years, 550 MACE endpoints

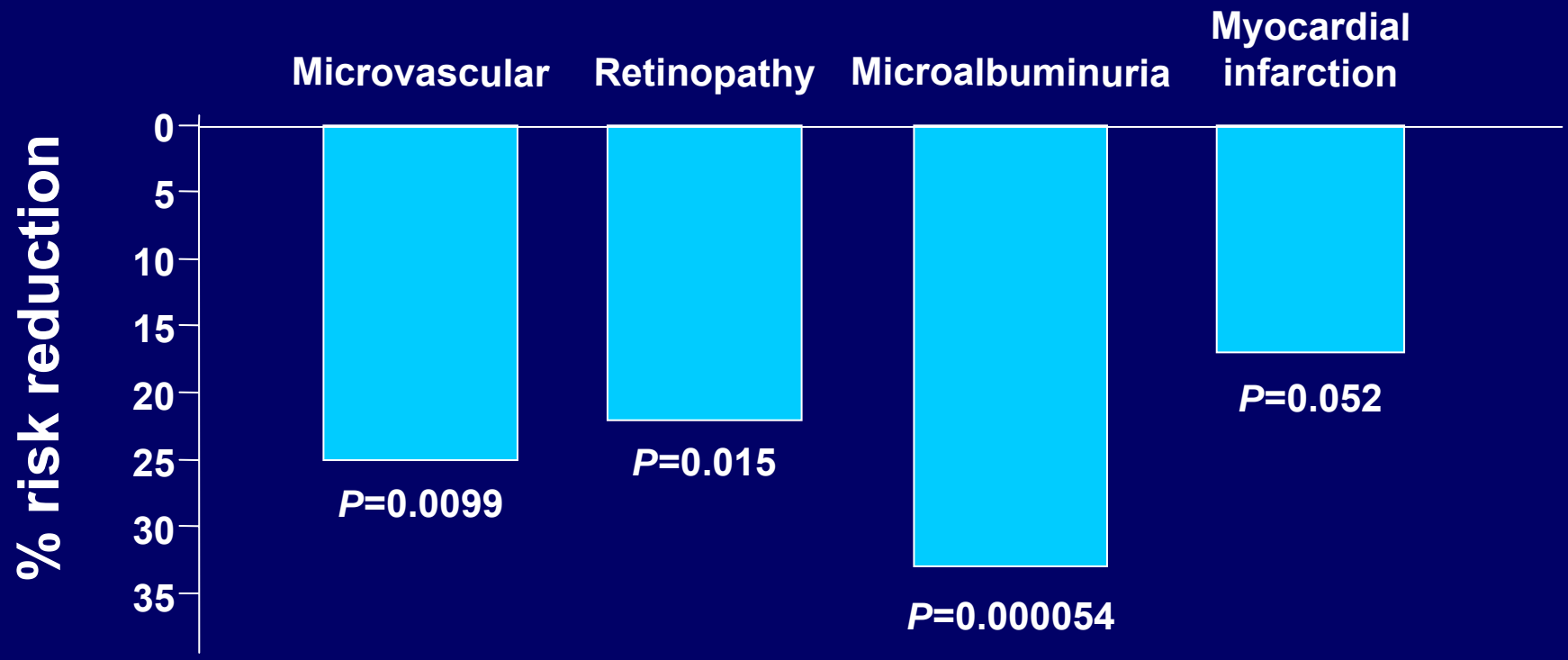


* Dates are LPLV

Questions for Today

- Is there an increase in the risk of cardiovascular mortality associated with rosiglitazone?
- Is there an increase in the risk of myocardial infarction associated with rosiglitazone?

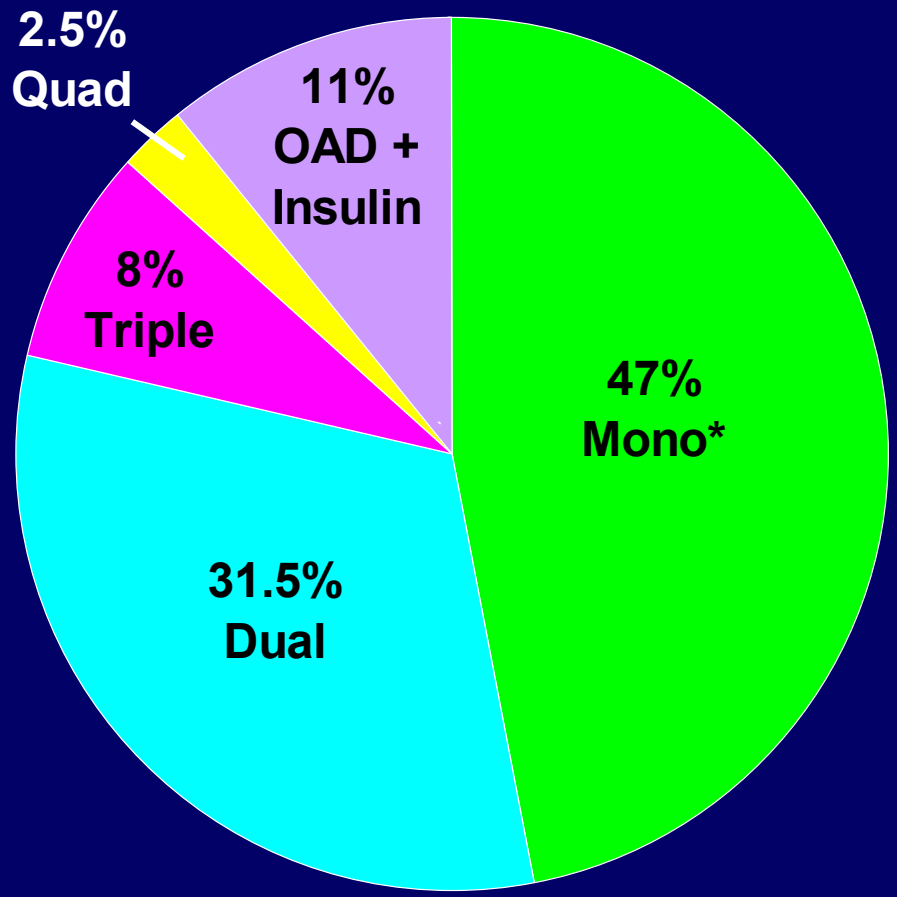
Benefits of Glycemic Control over 10-12 years



Adapted from UKPDS 33. *The Lancet* 1998;352:837-853

53% of Type 2 Diabetic Patients Are on Combination Therapy

Regimens by Therapy Type

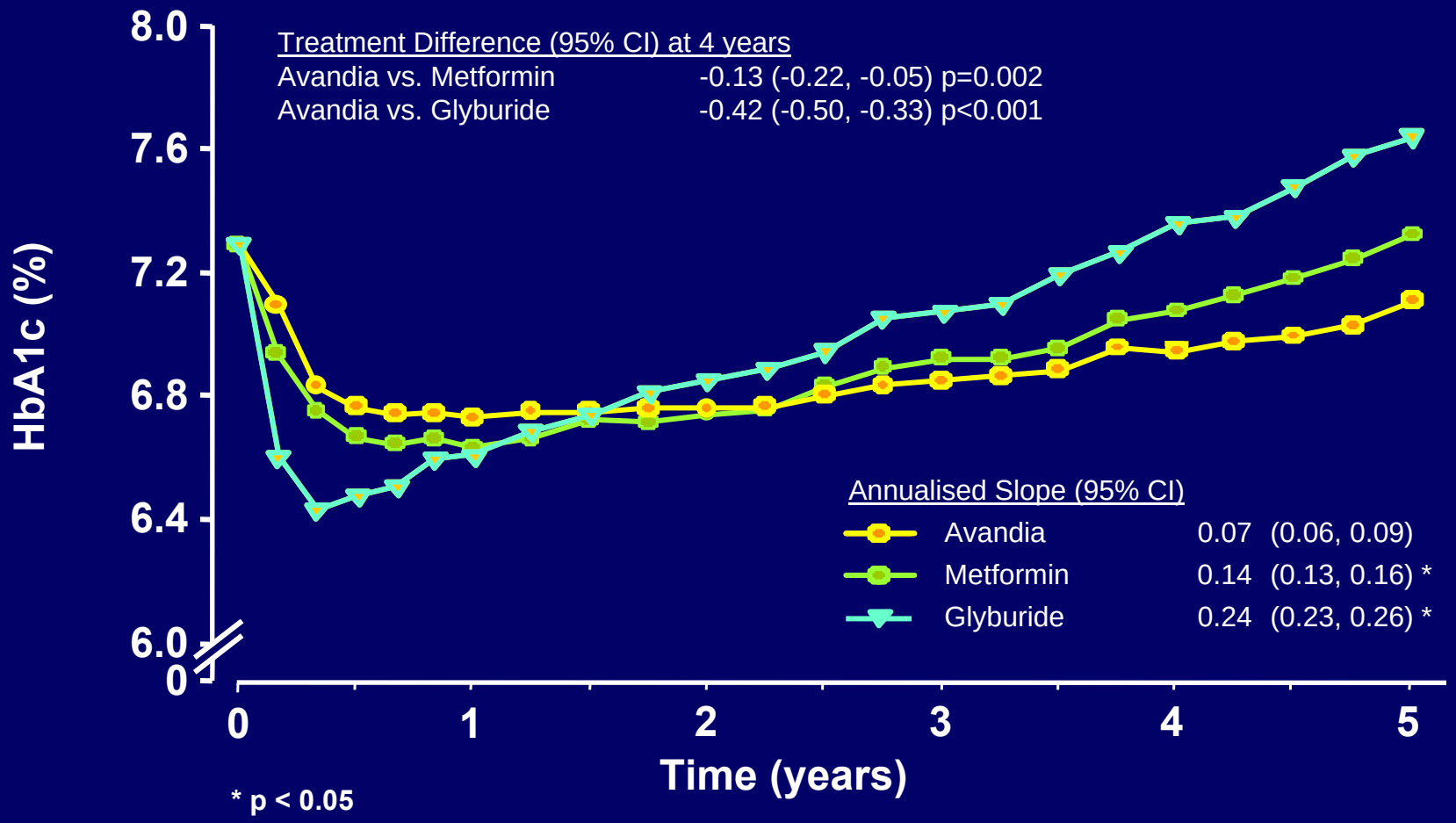


Total Combo = 53%

*Monotherapy includes Insulin alone

Source: Verispan Patient Level Data. Feb 2007 Regimen Report

ADOPT:
Sustained Reductions in HbA1c vs Metformin or Glyburide



Source: Kahn *NEJM* 2006; 355: 2427-2480

Considerations in the Choice of an Oral Agent

Drug Class	Route of Administration	Expected HbA1c Reduction (Monotherapy)	Side Effects
Sulfonylureas (SUs)	Oral	1.5%	Hypoglycemia, weight gain, probable cardiac ischemic risk with certain SUs
Biguanide/Metformin	Oral	1.5%	Rare lactic acidosis, contraindicated in patients with renal impairment
Alpha-glucosidase inhibitors	Oral	0.5 to 0.8%	GI side effects
TZDs/PPAR agonists	Oral	0.5 to 1.5%	Anemia, weight gain, edema, heart failure, cardiac ischemic risk; potential cancer risk (bladder cancer signal with pioglitazone)
DPPIV-inhibitors**	Oral	0.5 to 0.9%	Limited clinical experience; nonclinical safety signals for many in development

Abstracted from FDA Briefing Document

Recommendations

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US Regulatory Affairs
GlaxoSmithKline

External Experts

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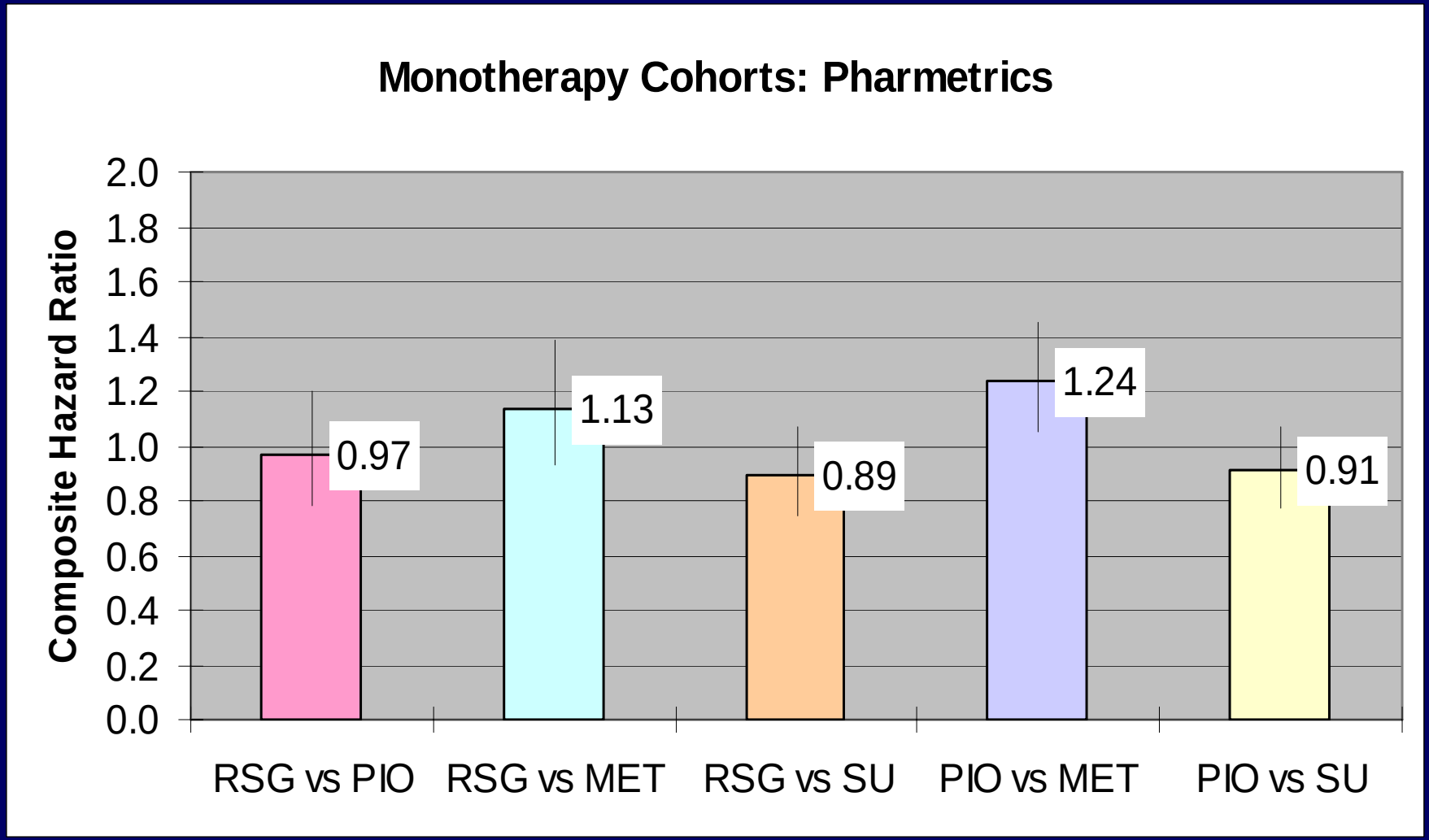
Clarifying Questions from the Committee

Distribution of MI SAEs in ADOPT Across Tertiles of Change in LDL at 6 Months

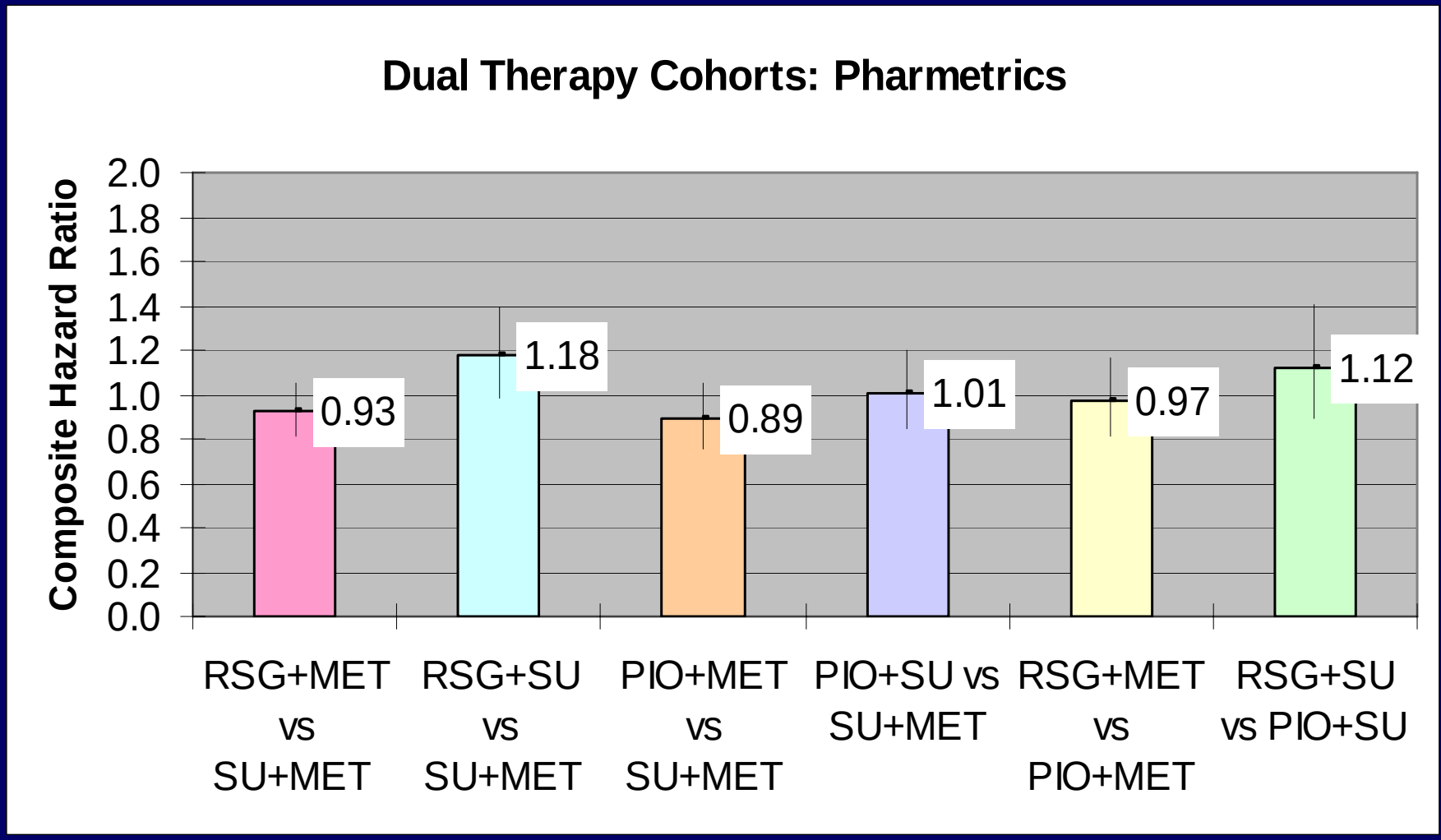
Tertile	Low	Middle	High
RSG N = 1456 Total w/MI = 24*	7 (2.0)	6 (1.6)	8 (2.1)
Metformin N = 1454 Total w/MI = 20*	9 (2.4)	4 (1.0)	2 (0.5)
GLY/GLIB N = 1441 Total w/MI = 14*	4 (1.1)	2 (0.5)	3 (0.8)

* 3(RSG), 5 (Met) and 5(GLY) had an MI and are missing an LDL value or the MI occurred prior to month 6

Hazard Ratios for Combined Outcome: Pharmetrics Report



Hazard Ratios for Combined Outcome: Pharmetrics Report (Cont)



Hazard Ratios for Combined Outcome: Pharmetrics Report (Cont)