

Comparative Effectiveness in Drug Development

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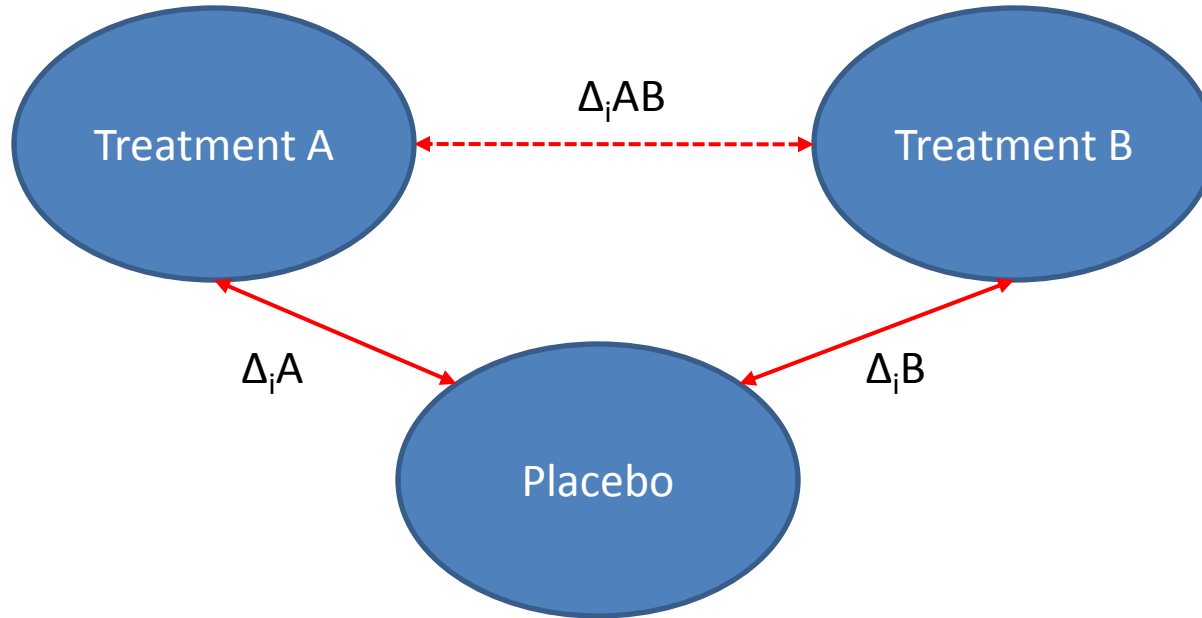
Comparative Effectiveness

Need: new treatment options need to be evaluated against other treatment options to quantify the benefits

- Patients, reviewers, payers
- Sponsor; development and investment decisions

Dilemma: most trials in drug development are placebo controlled or vs. standard of care (SOC)

=> Meta-analysis to provide an indirect comparison



Assumption: treatment effects are exchangeable between trials

Pooling data across trials with variability in patient/ trial characteristics

- Some variability between trials is expected due to the fact that a random sample of the patient population is evaluated
- If there is more variability than expected based on sample size and by chance alone, this is called **heterogeneity**
 - Study level covariates could explain between trial differences and normalize the outcomes for those differences, i.e. baseline disease severity
 - Random effects model can be used to account for unexplained between trial differences
 - Relative treatment effects may be reasonably constant across variability in trial characteristics

Model-Based meta-analysis

- Comparative Effectiveness vs. other treatment options from early development through approval and phase IV
 - Therapeutic Opportunity
- Increased precision in decision making by leveraging existing information
 - Similarities in DR within drug class
 - Similarities in PD drug interactions within drug class
 - Similarities in relationship across endpoints
 - Similarities in covariate relationships
- Scaling to other indications
 - Similarities in relative differences across all drugs or within class
 - Lack of difference
- Scaling from biomarker to clinical endpoints
- Optimize Trial design
 - Impact of trial design features on placebo, treatment effect and variability

Anticoagulants

- VTE prevention after hip/ knee replacement
 - Database: 89 trials, >92,000 patients, 23 drugs and 7 drug classes: LMWH, direct and indirect FXa inhibitors, univalent and bivalent Thrombin inhibitors, Heparin, Warfarin
 - Enoxaparin (standard of care) included in 54 trials
- Efficacy: joint analysis of total VTE, major VTE, and PE
- Safety: joint analysis of major bleeding, CRNM, and total bleeding
- Expanded to other indications: VTE treatment, AF, ACS

General Analysis Methodology

- Joint analysis of k endpoints to estimate the dose response relationship for each drug for each endpoint, accounting for correlation
- Primary response variable was number of patients with an event during the treatment period. Patient variability follows a binomial distribution:

$$N_{event,kij} \sim \text{binomial}(P(event)_{kij}, N_{kij})$$

- Probability of a patient having an event for endpoint (k) in a treatment arm (j) of a trial (i) is a function of a placebo response for that endpoint in that trial ($E_{0,ki}$) and a dose response relationship for the treatment effect for the endpoint ($g(x)_k$), including covariates X_{ij}

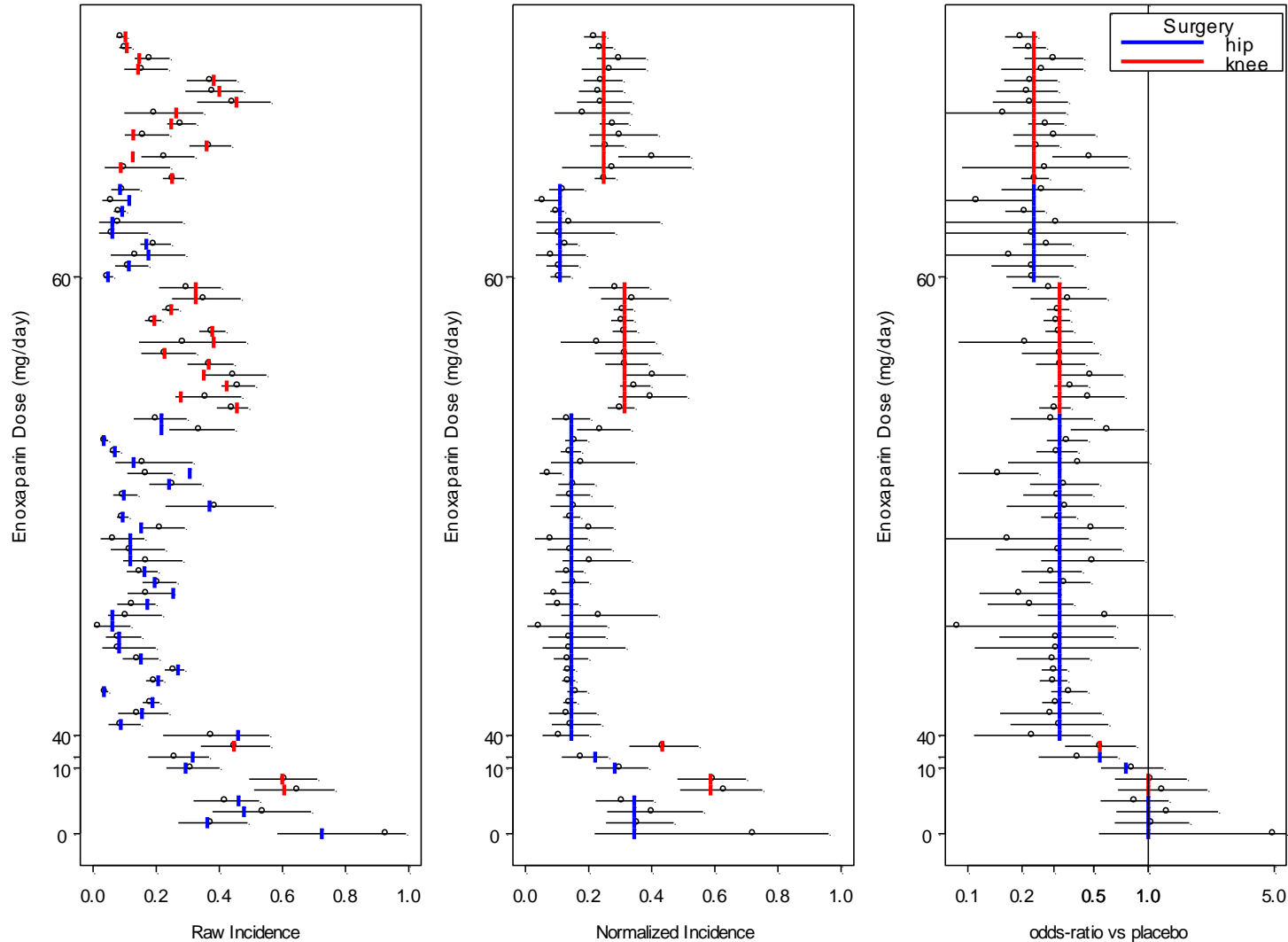
$$P(event)_{kij} = f\{E_{0,ki} - g(Drug_{ij}, Dose_{ij}, X_{ij}, \theta_i)_k\}$$

- The trial specific model parameters θ_{kj} are assumed to be normally distributed with between trial variance Ω (heterogeneity)

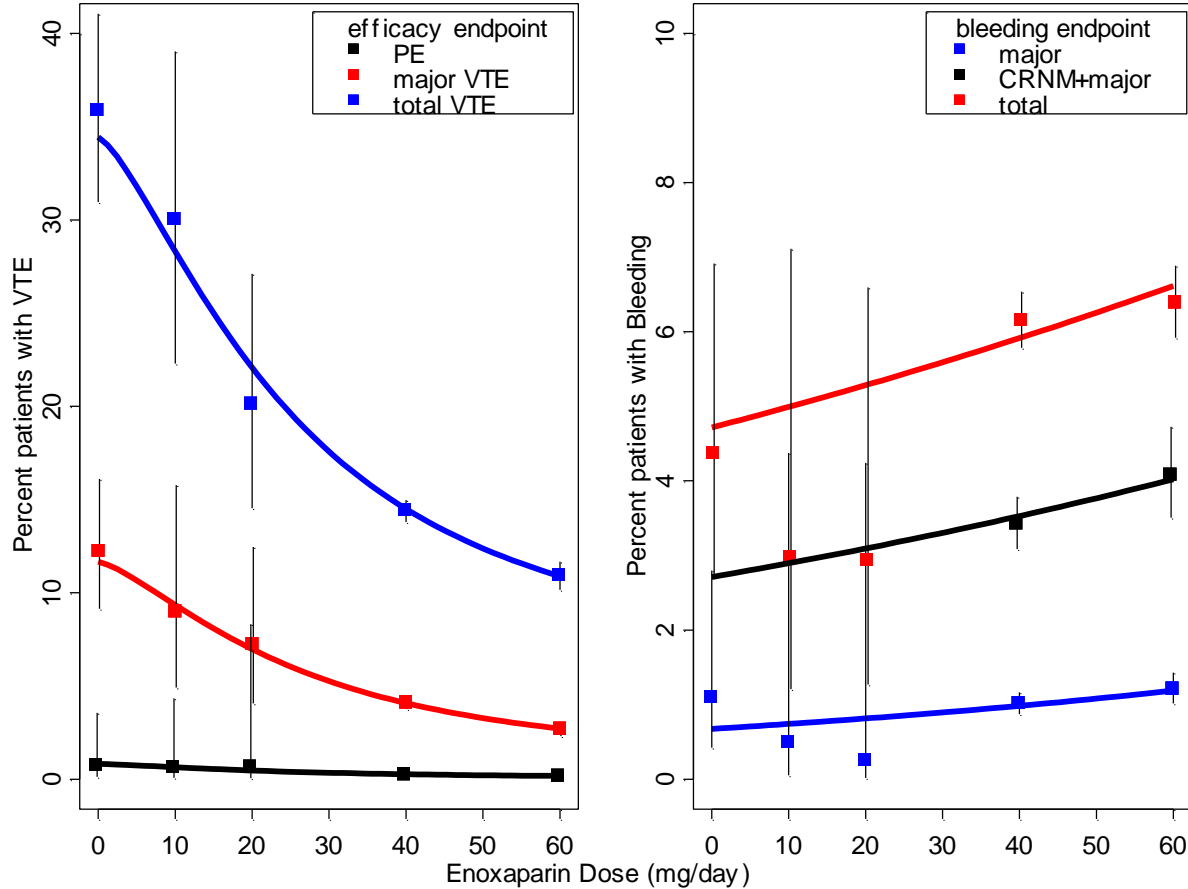
$$\theta_{kj} \sim N(\theta_k, \Omega)$$

There is a large between trial variability in absolute incidence of VTE but little variation in relative effect

total VTE for Enoxaparin

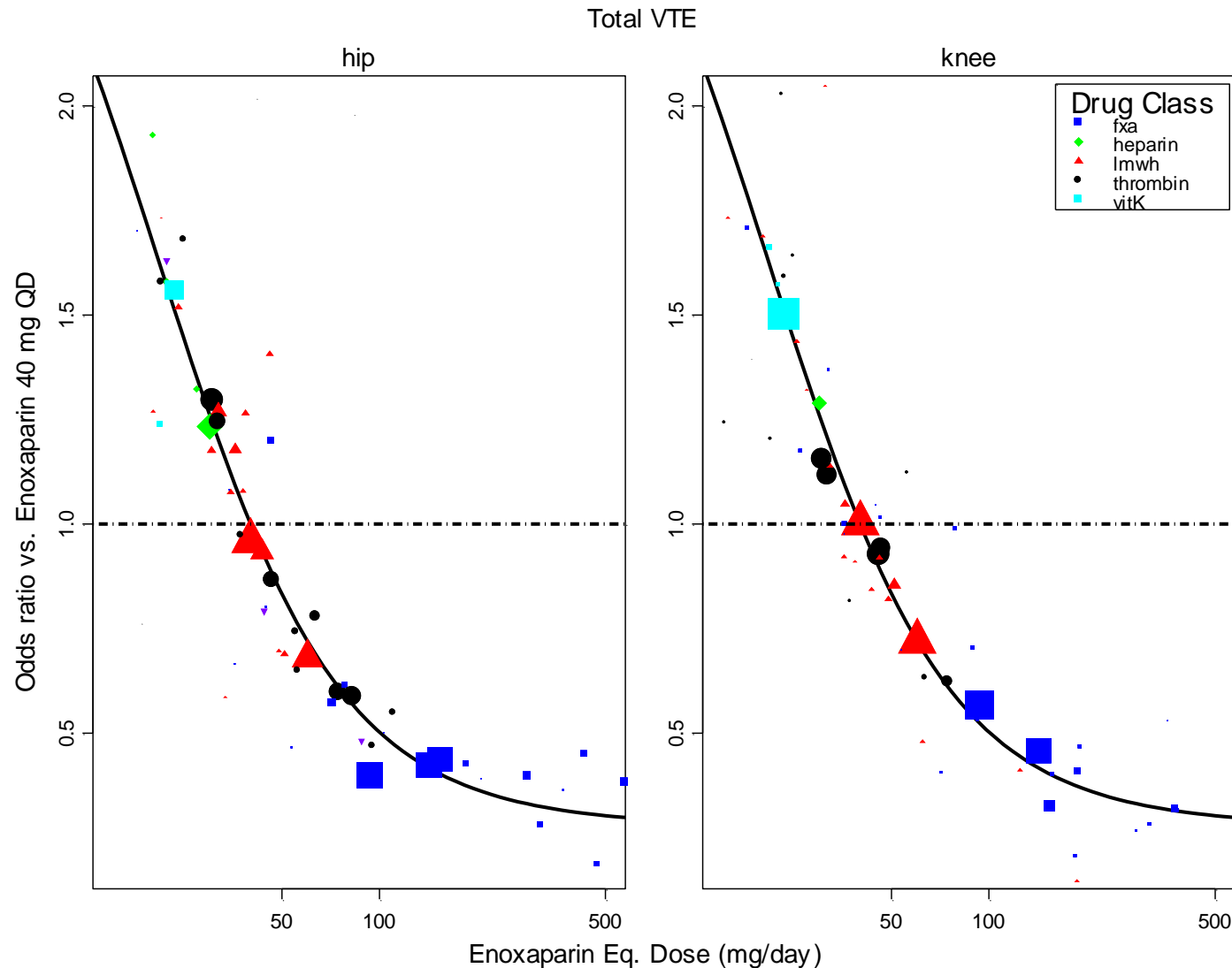


Dose response analysis of standard of care Enoxaparin shows a significant difference between 40 mg QD and 30 mg BID for efficacy and bleeding



Relative risk 30 mg BID vs. 40 mg QD [95%CI]	
Total VTE	0.75 [0.72 to 0.78]
Major VTE	0.67 [0.62 to 0.71]
Major bleeding	1.21 [1.16 to 1.27]
CRNM bleeding	1.14 [1.1 to 1.19]
Total bleeding	1.12 [1.09 to 1.15]

There was no significant difference in treatment response between hip and knee surgery



How to quantify relative effectiveness of anticoagulants?

- Therapeutic Index (TI):

$$TI = \frac{\text{Dose with acceptable bleeding}}{\text{Dose with relevant risk reduction for VTE}}$$

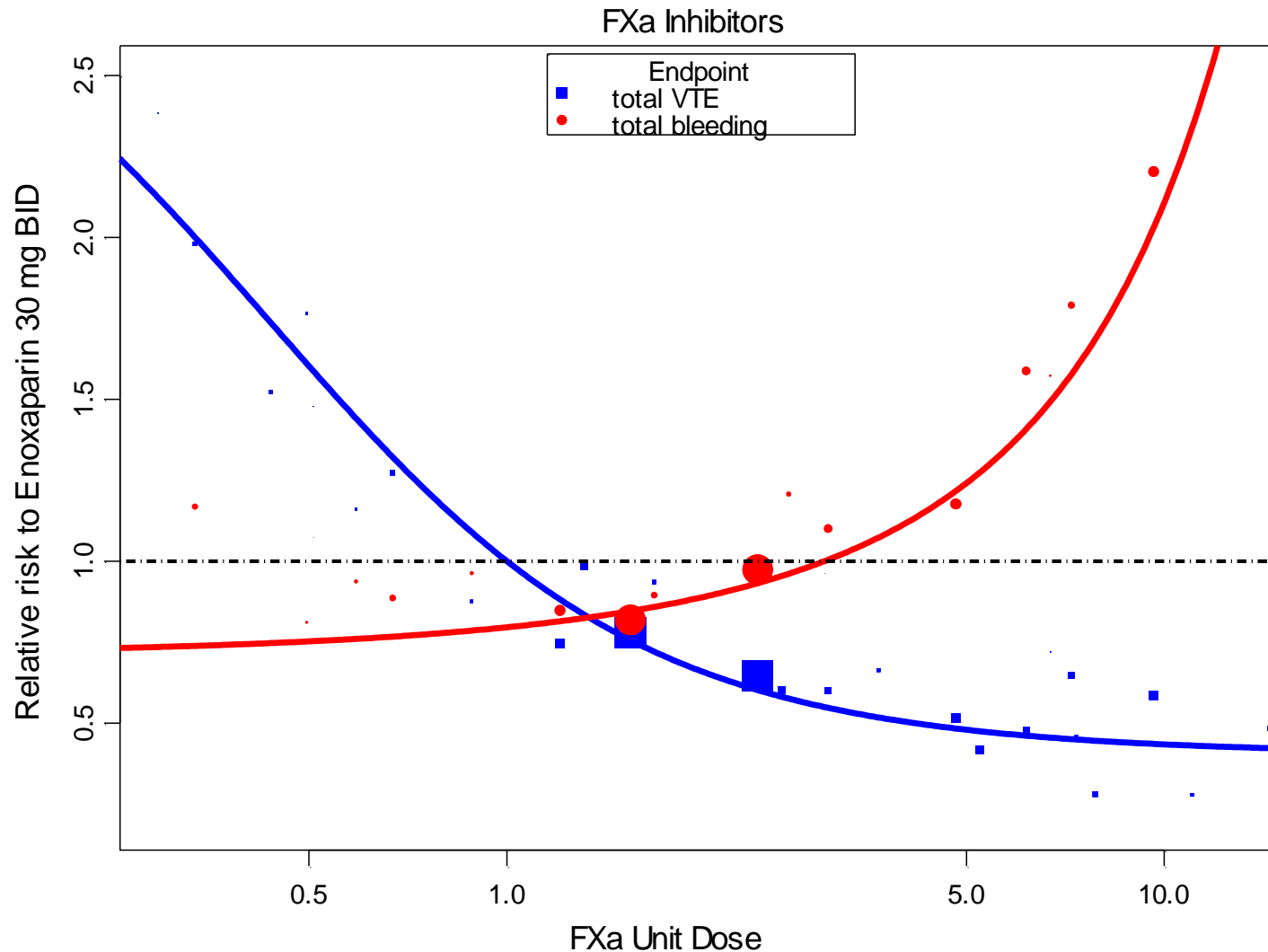
- Relative TI:

- Relative TI = TI / TI_{SOC}

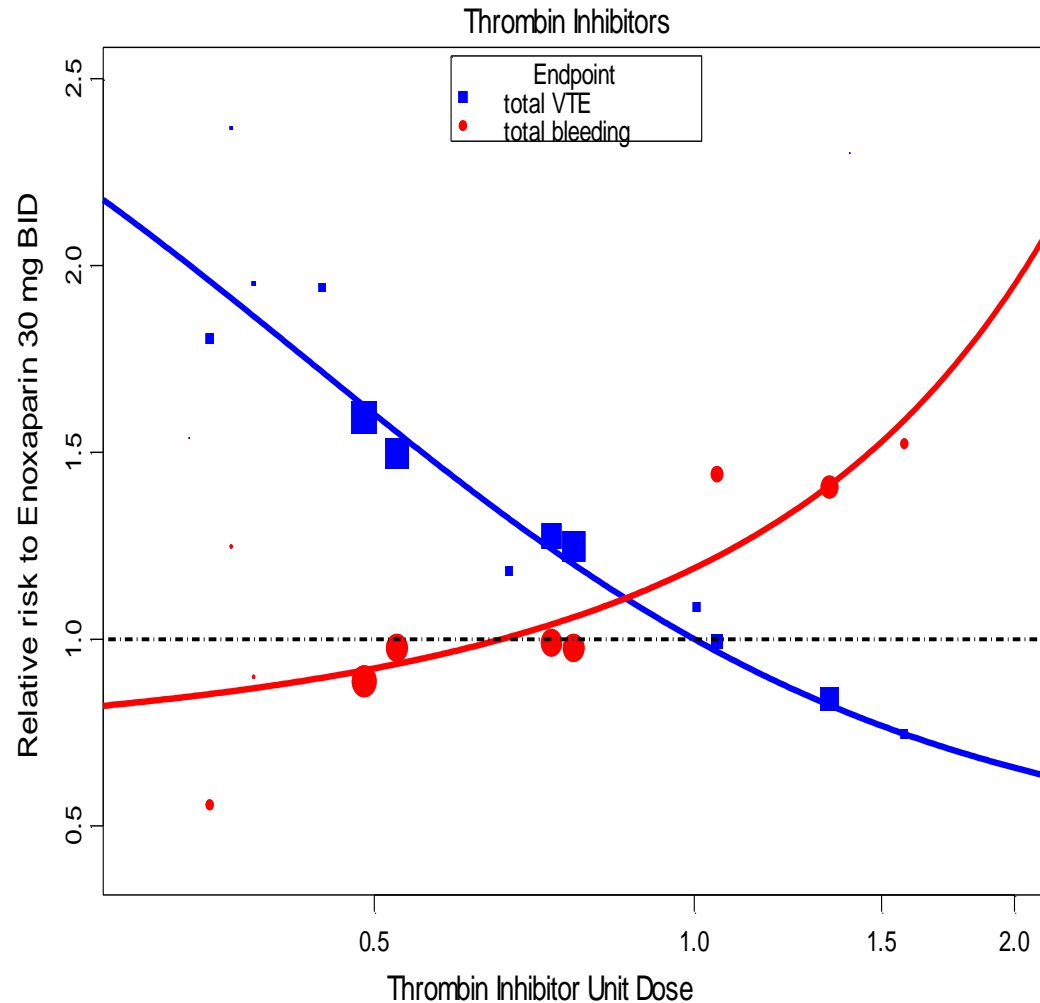
- The anticoagulants were found to differ only in potency for both efficacy and bleeding, therefore:

- Relative TI = $\frac{ED_{50}\text{bleeding} * ED_{50}\text{efficacy,SOC}}{ED_{50}\text{efficacy} * ED_{50}\text{bleeding,SOC}}$

The FXa inhibitors had a significantly wider Therapeutic Index when compared to Enoxaparin



Whereas Thrombin inhibitors had a smaller therapeutic index when compared to Enoxaparin



Drug Class	TI Total VTE vs. total bleeding	TI Major VTE vs. major bleeding
FXa direct (Apixaban, Rivaroxaban, etc.)	3 [2.3 to 4]*	2.3 [1.7 to 3.2]*
Thrombin univalent (Dabigatran, etc.)	0.66 [0.53 to 0.82]*	0.84 [0.64 to 1.1]

*p<0.05; [95% CI]

Summary Anticoagulants

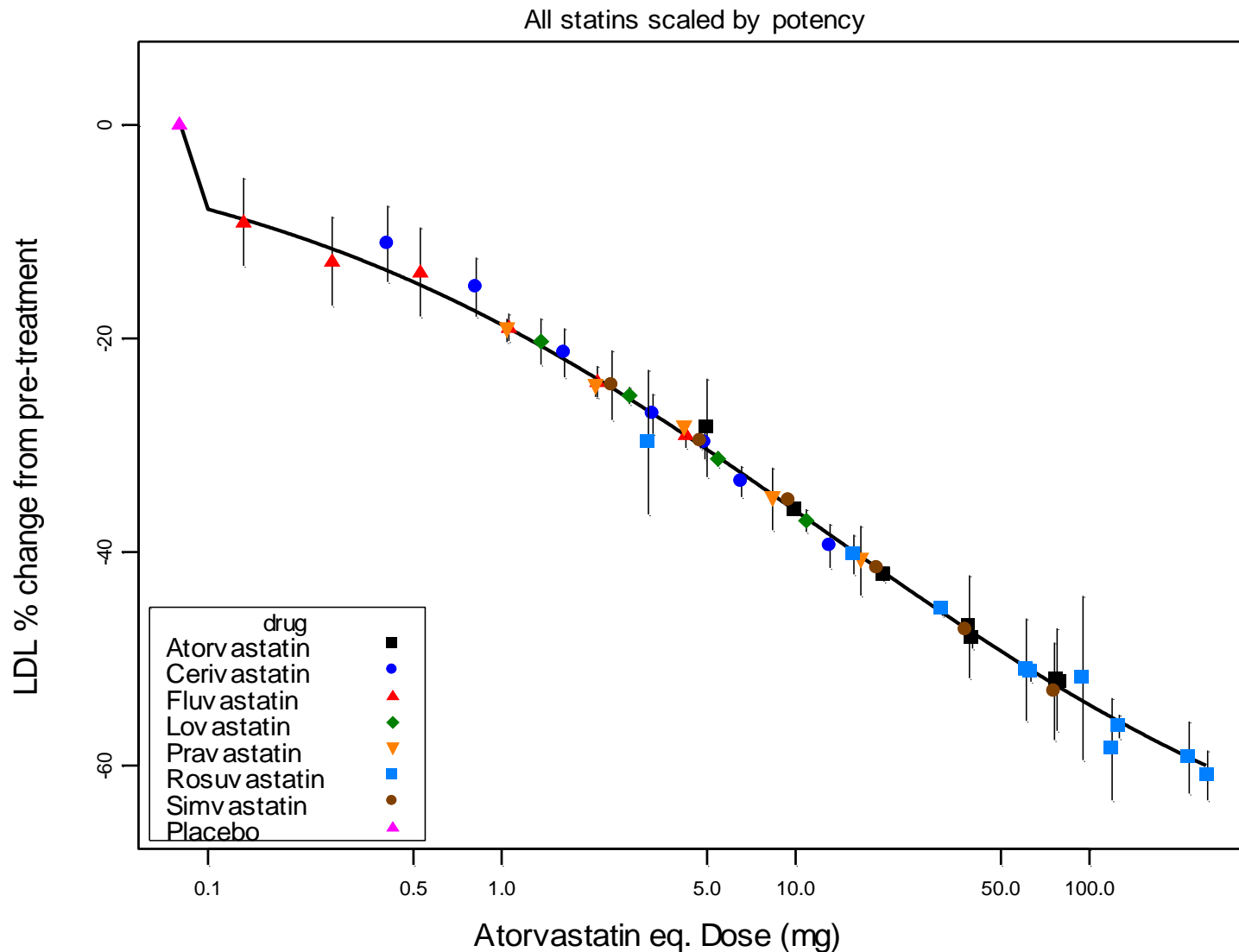
- Quantified difference between US (30 mg BID) and EU (40 mg QD) dose regimens of standard of care
- Showed that relative effect between two treatment options is the same in hip and knee replacement.
- Quantified benefit of FXa inhibitors over SOC and other treatment options such as Thrombin Inhibitors
- Identified optimal dose window for FXa Inhibitors

Dyslipidemia

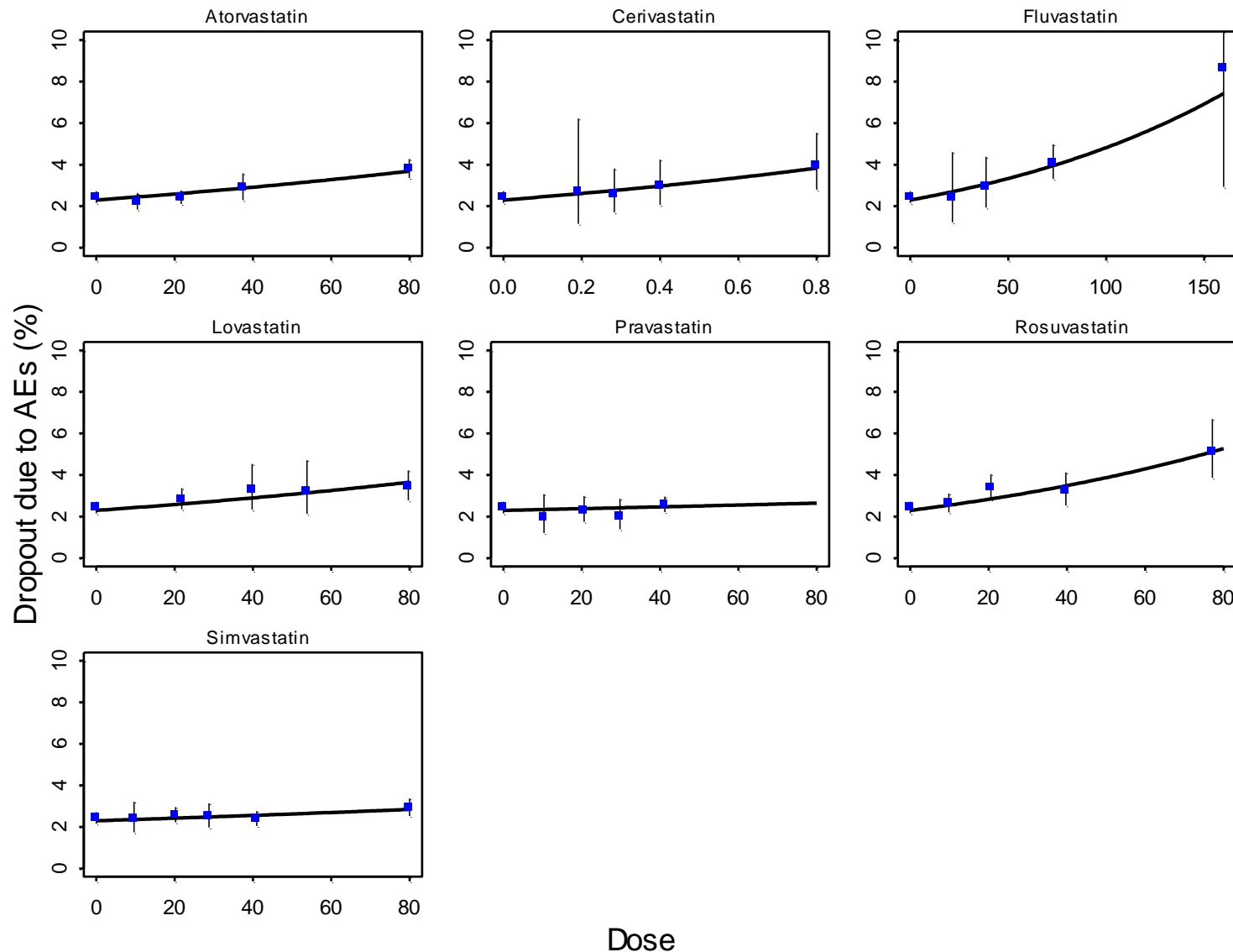
Database with about 450 trials that captures summary level data from publicly available data sources for the following outcomes:

- atherogenic lipid profile and inflammatory biomarkers: LDL, Triglycerides, HDL, total cholesterol, ApoA1, ApoB, CRP, nHDL.
- adverse events: dropout, dropout due to AEs, risk in ALT/AST elevation, CPK elevation, myalgia, myopathy, etc.
- progression of atherosclerosis (QCA, Bmode, or IVUS): mean and min lumen diameter, % stenosis; mean and max IMT, plaque volume, plaque burden, etc.
- cardiovascular outcomes: major coronary events, cardiovascular events, stroke, MI, hospitalization due to UA, PCI, etc.

After adjusting for differences in potency (ED50) all statins share a common dose response relationship for LDL



Statin Dose response relationship for AE related dropouts

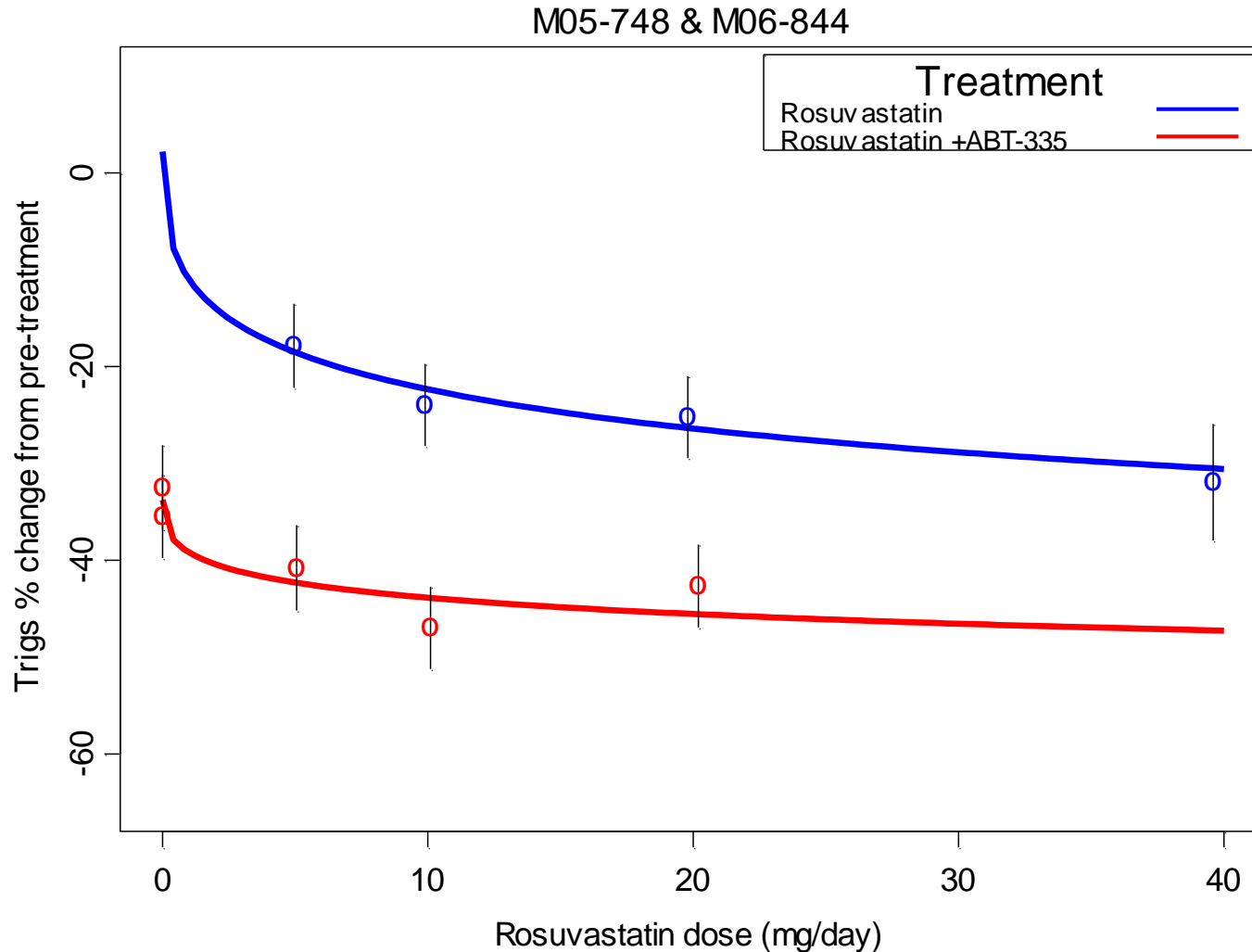


The Statins differ with respect to their benefit/risk ratio

Drug	ALT/ AST Elevations	AE dropout
	ED50 LFT/ ED50 LDL	ED50 dropout/ ED50 LDL
Fluvastatin	0.48 [0.27 to 0.88]	0.75 [0.47 to 1.2]
Cerivastatin	0.83 [0.41 to 1.7]	2 [0.69 to 6]
Lovastatin	1.3 [0.86 to 1.9]	2.6 [1.7 to 4]
Pravastatin	2.6 [0.79 to 8.4]	4.7 [0.94 to 24]
Atorvastatin	3.6 [2.7 to 4.9]	13 [8.8 to 20]
Simvastatin	4.3 [2.9 to 6.6]	14 [6.3 to 32]
Rosuvastatin	13 [8.3 to 22]	24 [15 to 38]

- For drugs with the same E_{max} , the ratio of the ED_{50} for safety and efficacy is a good measure to compare their therapeutic index (TI)
- Rosuvastatin provides the widest safety margin and Fluvastatin the smallest

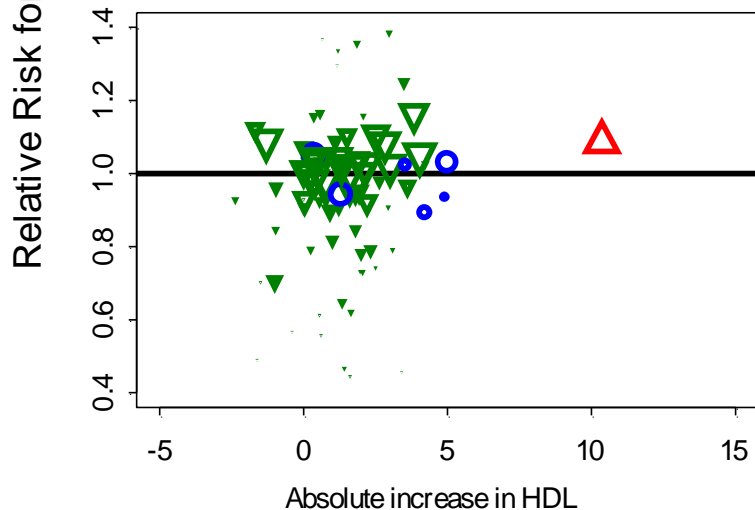
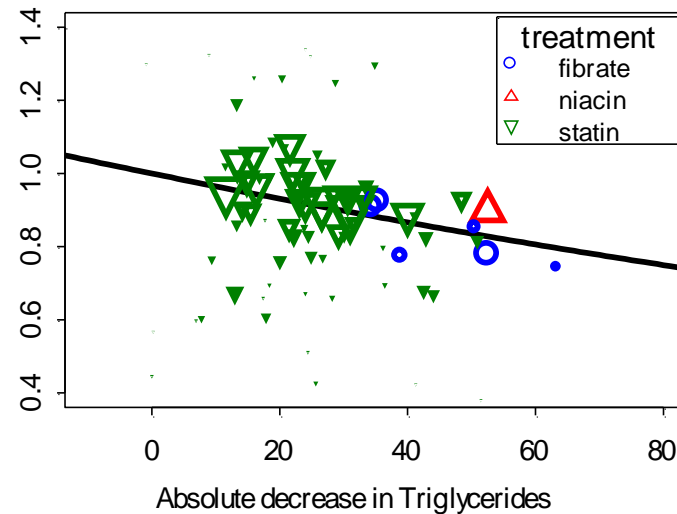
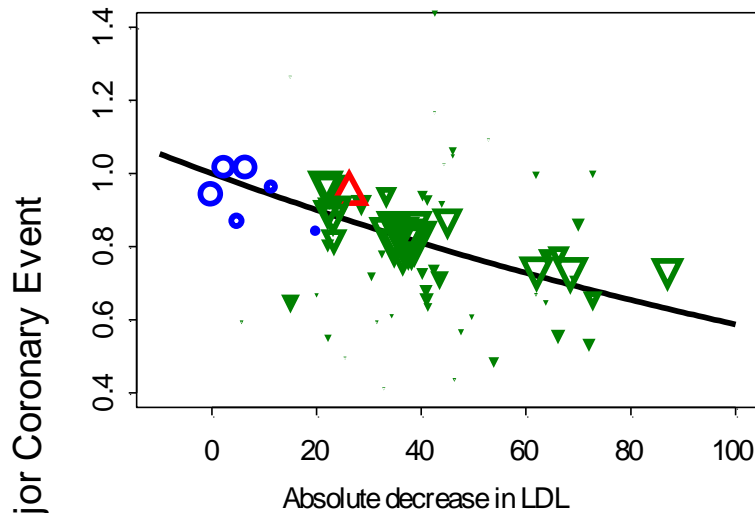
The analysis was used to characterize the interaction between fenofibric acid and statins



What is the benefit of Triglyceride lowering on top of LDL lowering?

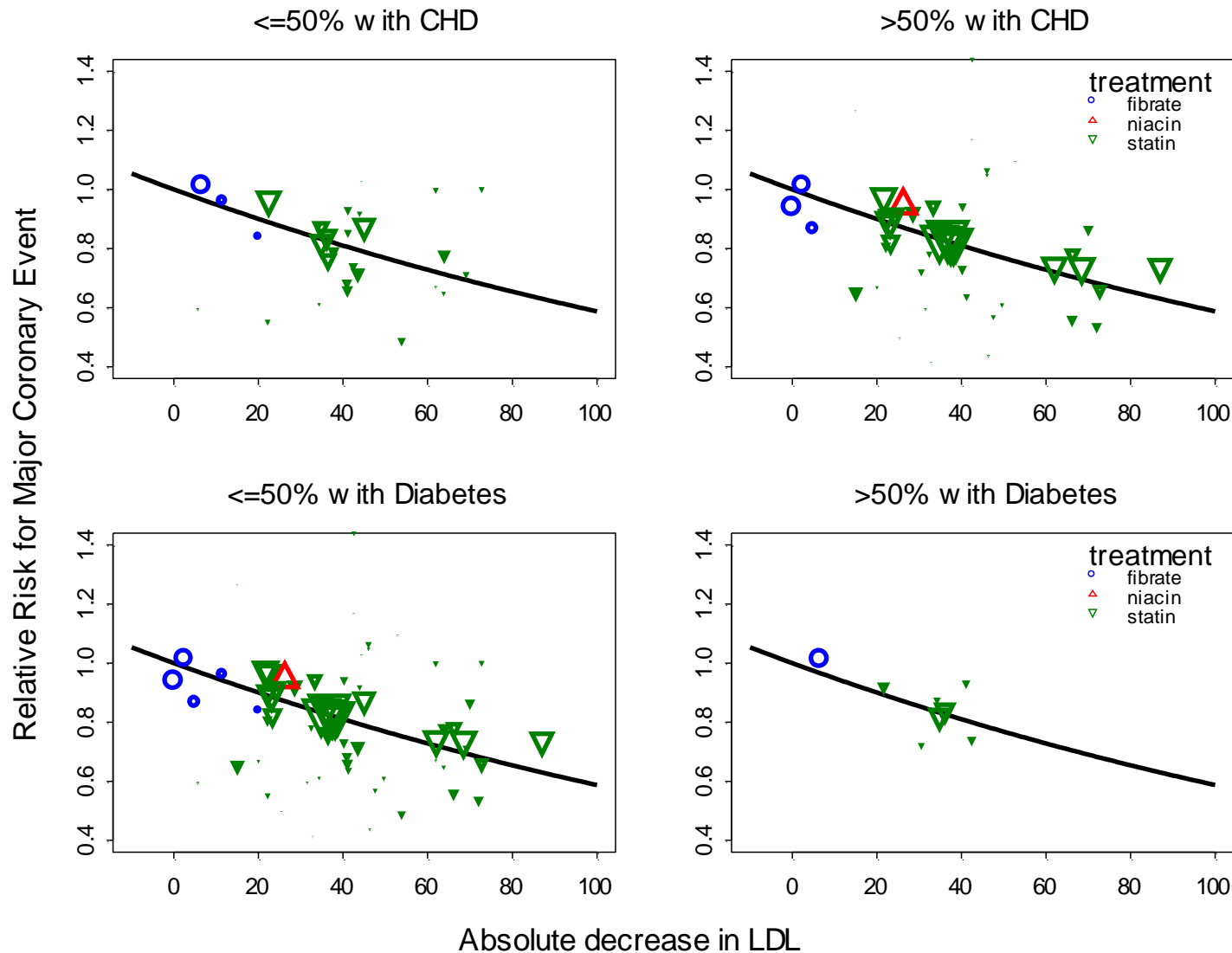
- Database was used to characterize the multivariate relationship between changes in LDL, HDL and triglycerides and risk for **major coronary events** after treatment with statins, fibrates or niacin.

The meta-analysis found a significant contribution of lowering triglycerides on top of reducing LDL-C to the risk reduction for a major coronary event after treatment with statins, fibrates or niacin ($p < 0.001$).



- The risk reduction for major coronary events was estimated to be 18.5% [14.1 to 22.7%] for every 1 mmol/L (38.7 mg/dL) reduction in LDL-C and 27.5% [15.7 to 37.7%] for every 1 mmol/L (88.6 mg/dL) reduction in triglycerides.
- The reduction in triglycerides was found to explain most (84%) of the risk reduction for treatment with fibrates. For statins, the reduction in LDL-C was found to explain most (71%) of their benefit.

The risk reduction per unit change in LDL-C and triglycerides was not dependent on age, gender, diabetes and prior CHD and was not different between fibrates and statins.



Summary Dyslipidemia

- Quantified risk/benefit of statins and fibrates
- Characterized the pharmacodynamic interaction between fibrates and statins across all lipid endpoints
- Quantified the relationship between lipid changes and cardiovascular risk reduction
 - Established importance of triglycerides in addition to LDL

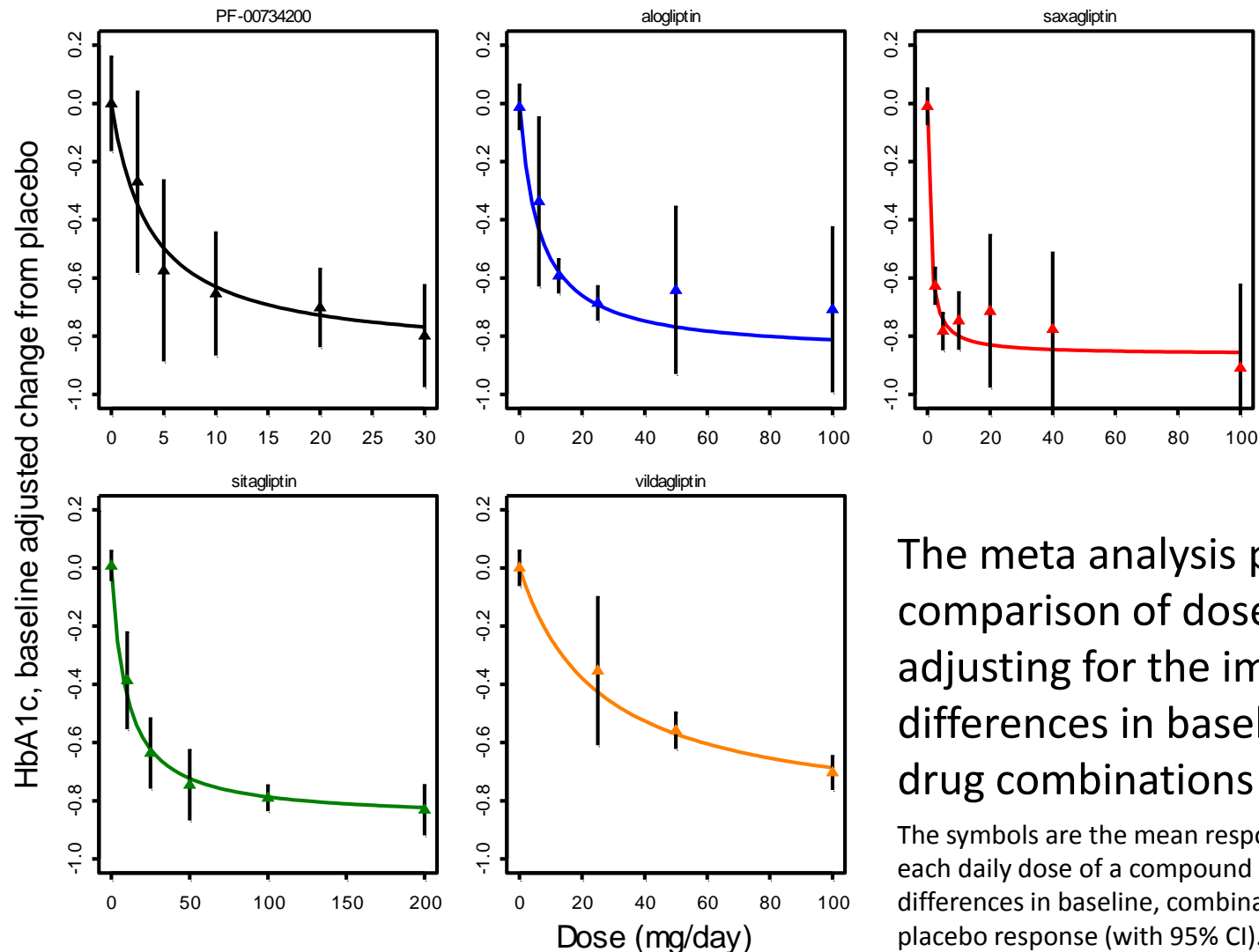
Diabetes

- A meta-analysis was completed of all trials that evaluated DPP-IV inhibitors as mono-therapy and combination therapy with metformin, sulfonylureas (glyburide and glimepride), insulin, and thiazolidinediones (pioglitazone and rosiglitazone)
- **29 trials:** PF-00734200 (2), alogliptin (6), saxagliptin (5), sitagliptin (7), and vildagliptin (9)
- **103 treatment arms:** PF-00734200 (8), alogliptin (21), saxagliptin (22), sitagliptin (24), and vildagliptin (28)
- **12,370 patients:** PF-00734200 (573), alogliptin (2483), saxagliptin (2853), sitagliptin (3786), and vildagliptin (2675)
- **5 treatment paradigms:** mono-therapy (12 trials), + insulin (2), + metformin (7), + sulfonylureas (4), + thiazolidinediones (4)

DPP-IV dose response

- There was a significant difference in E_{\max} for the different combination therapies ($p=0.0034$)
 - Largest difference is for combination therapy with Insulin: a 46% [25 to 68%; 90%CI] decrease in E_{\max} relative to monotherapy
- There was no significant difference in E_{\max} for the different drugs ($p=0.59$)
 - Largest difference is for Alogliptin (smallest E_{\max}) and Vildagliptin (largest E_{\max})
- There was a significant increase in E_{\max} (larger difference from placebo) with increasing baseline ($p=0.035$)
 - There is a 42% [5 to 80%; 90%CI] increase in E_{\max} for a 1% difference in baseline HbA1c

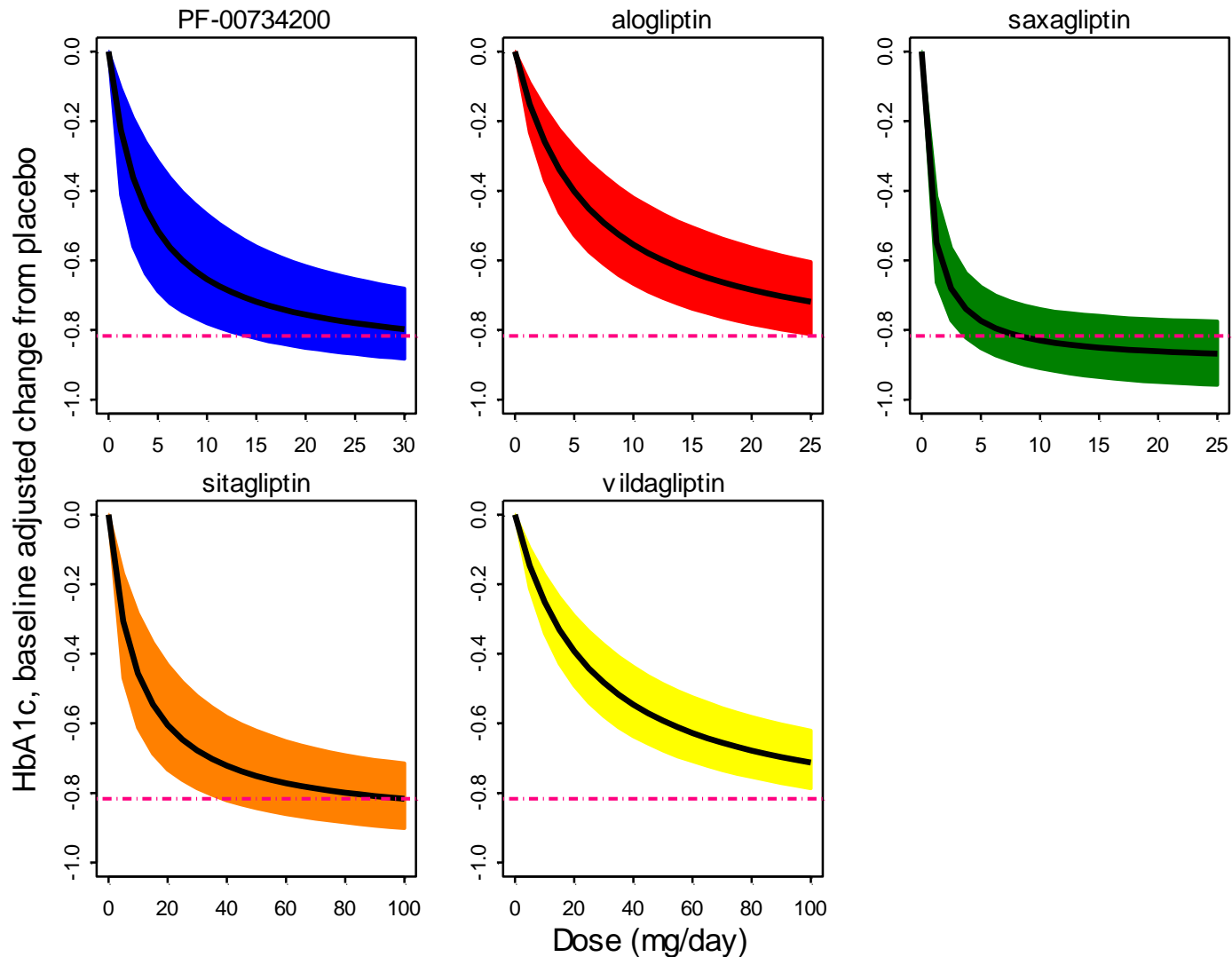
DPP-IV dose response adjusted for metformin combination therapy



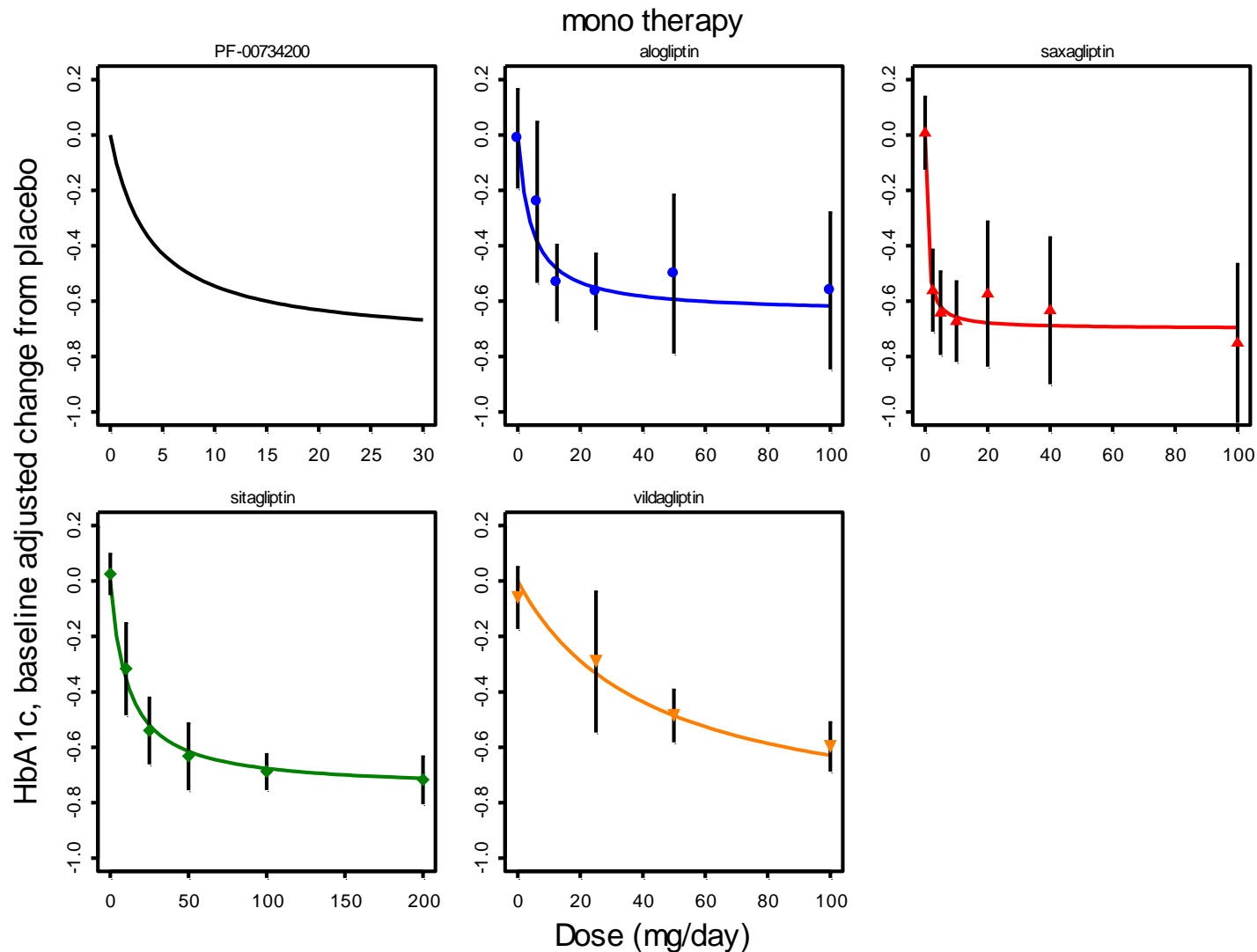
The meta analysis provided a comparison of dose response after adjusting for the impact of differences in baseline HbA1c and drug combinations across the trials.

The symbols are the mean response across all trials for each daily dose of a compound after adjustment for differences in baseline, combination treatment, and placebo response (with 95% CI).

Predicted dose response (90% CI) for metformin combination therapy (dashed line is sitagliptin 100 mg)



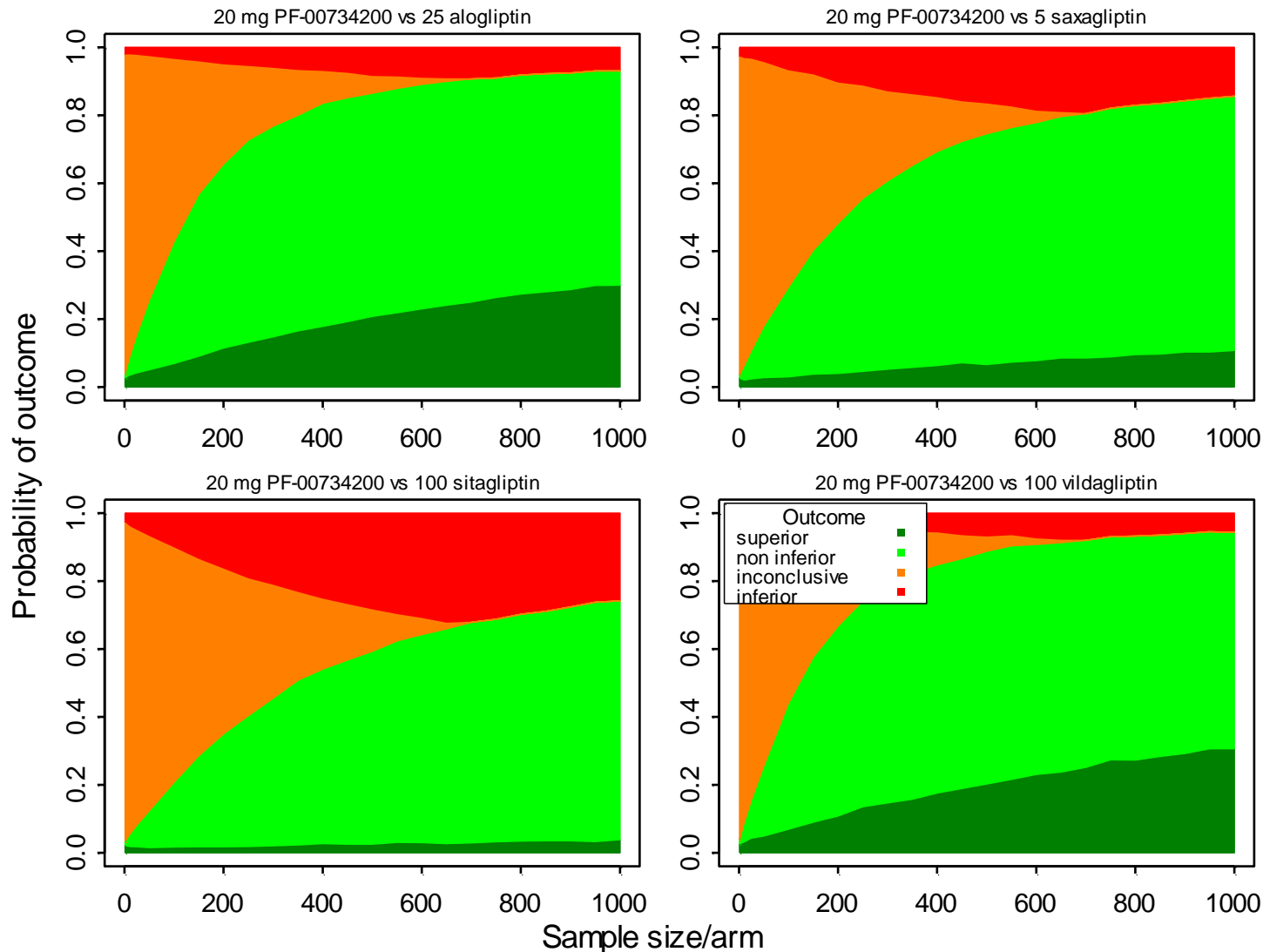
The model was used to predict the effect in indications that have not been evaluated such as Mono Therapy



The model was used to predict probability of outcomes for head-to-head trials

- 10,000 trials were simulated using the probability distribution of the difference between PF-00734200 and other treatments
- For each simulated trial the 95% CI (two-sided) of the difference between the two treatments was calculated
- The outcome was classified as:
 - Superior if upper 95%CI < 0 (PF-00734200 is significantly better than other treatment). Dark green area
 - Non-inferior if upper 95%CI < 0.2 (note that non-inferiority is at 2.5% level). Dark green + light green area (anything superior is also non-inferior)
 - Inferior if lower 95% CI > 0 and upper 95%CI > 0.2 (if significantly worse than competitor but also non-inferior is not classified as inferior). Red area
 - Inconclusive is none of the above. Orange area

The model was used to predict probability of outcomes for head-to-head trials



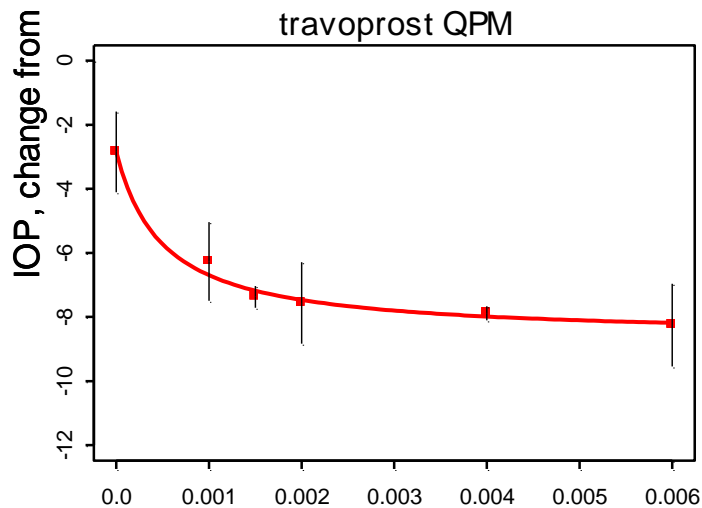
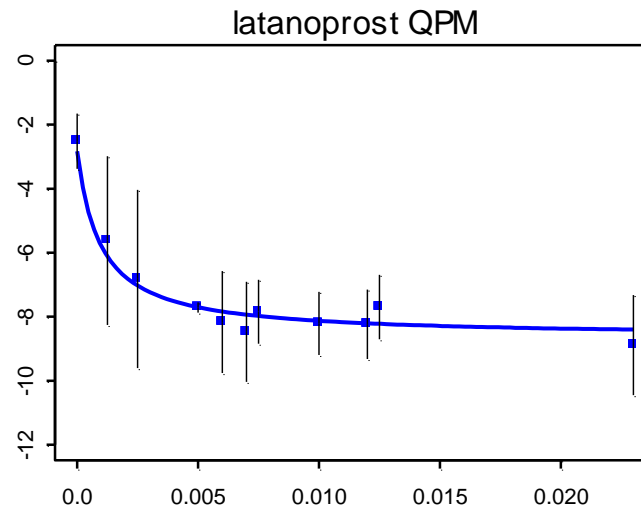
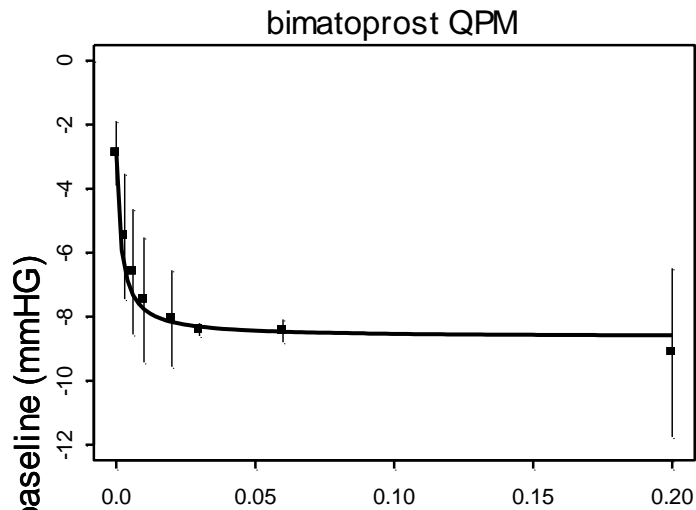
Summary Diabetes

- Quantified relative efficacy of DPP-IV inhibitors
- Reduced uncertainty in DR of novel compound due to similarities in DR across DPP-IV inhibitors
- Quantified the impact of between trial differences in baseline HbA1c
- Quantified differences in DR across indications such as mono-therapy and combination therapy with metformin, sulfonylureas, insulin, and thiazolidinediones to predict outcome of novel compound in indications that have not been evaluated yet.
- Calculated probability of success in head-to-head comparator trials

Glaucoma

- A meta-analysis of 59 clinical trials was completed to characterize the 24 hour dose response relationship for intra-ocular pressure (IOP) in patients with glaucoma or ocular hypertension
 - prostaglandin analogues (latanoprost, bimatoprost, and travoprost), beta-blockers (timolol), and carbonic anhydrase inhibitors (dorzolamide)
 - The IOP model captured the impact of dose, regimen, time after dose, time of day (clock time), and baseline IOP on the dose response relationships
 - >13,500 patients, 163 treatment arms and 1361 observations
- A meta-analysis of 26 clinical trials was completed to characterize the dose response relationship for hyperemia of prostaglandin analogues in patients with glaucoma or ocular hypertension
- The models were updated with data from a phase II trial of PF-03187207, a drug with a novel mechanism of action, to determine the drug's potential

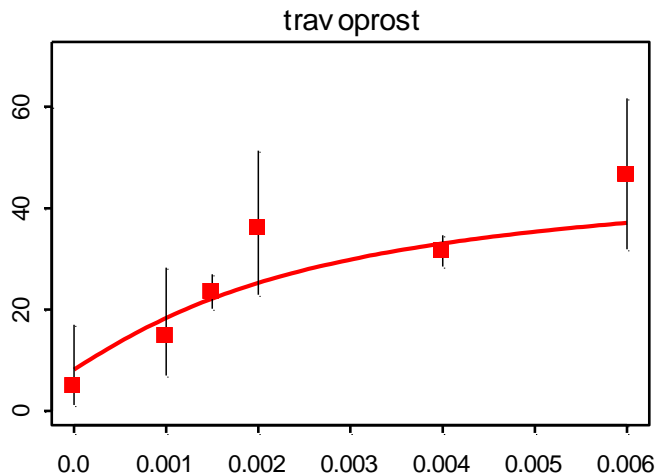
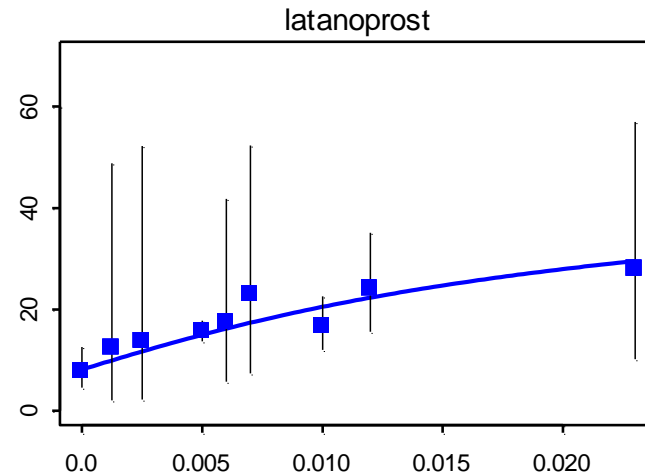
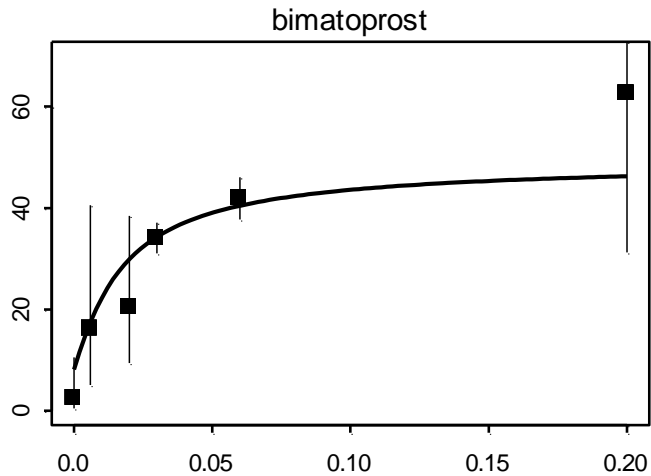
Prostaglandins share a similar dose response for IOP, differing only in potency



Drug	ED ₅₀ IOP %
latanoprost	0.00096 [0.00071 to 0.0013]
bimatoprost	0.0018 [0.00090 to 0.0035]
travoprost	0.00050 [0.00038 to 0.00066]

Total Daily Dose

Prostaglandins share a similar dose response for hyperemia, differing only in potency



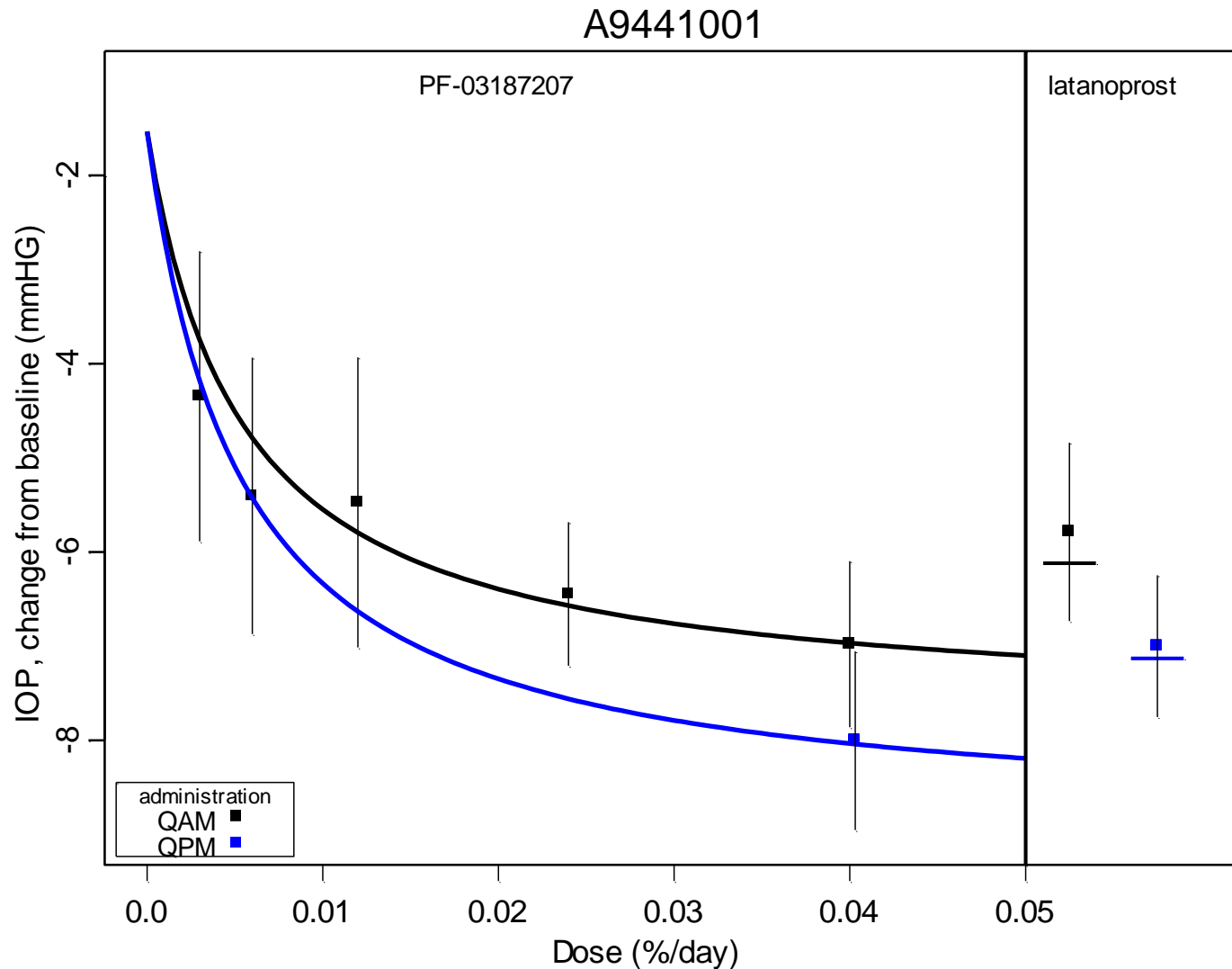
Drug	ED ₅₀ hyperemia
latanoprost	0.012 [0.0066 to 0.023]
bimatoprost	0.010 [0.0050 to 0.023]
travoprost	0.0016 [0.00081 to 0.0031]

The prostaglandins differ in therapeutic index

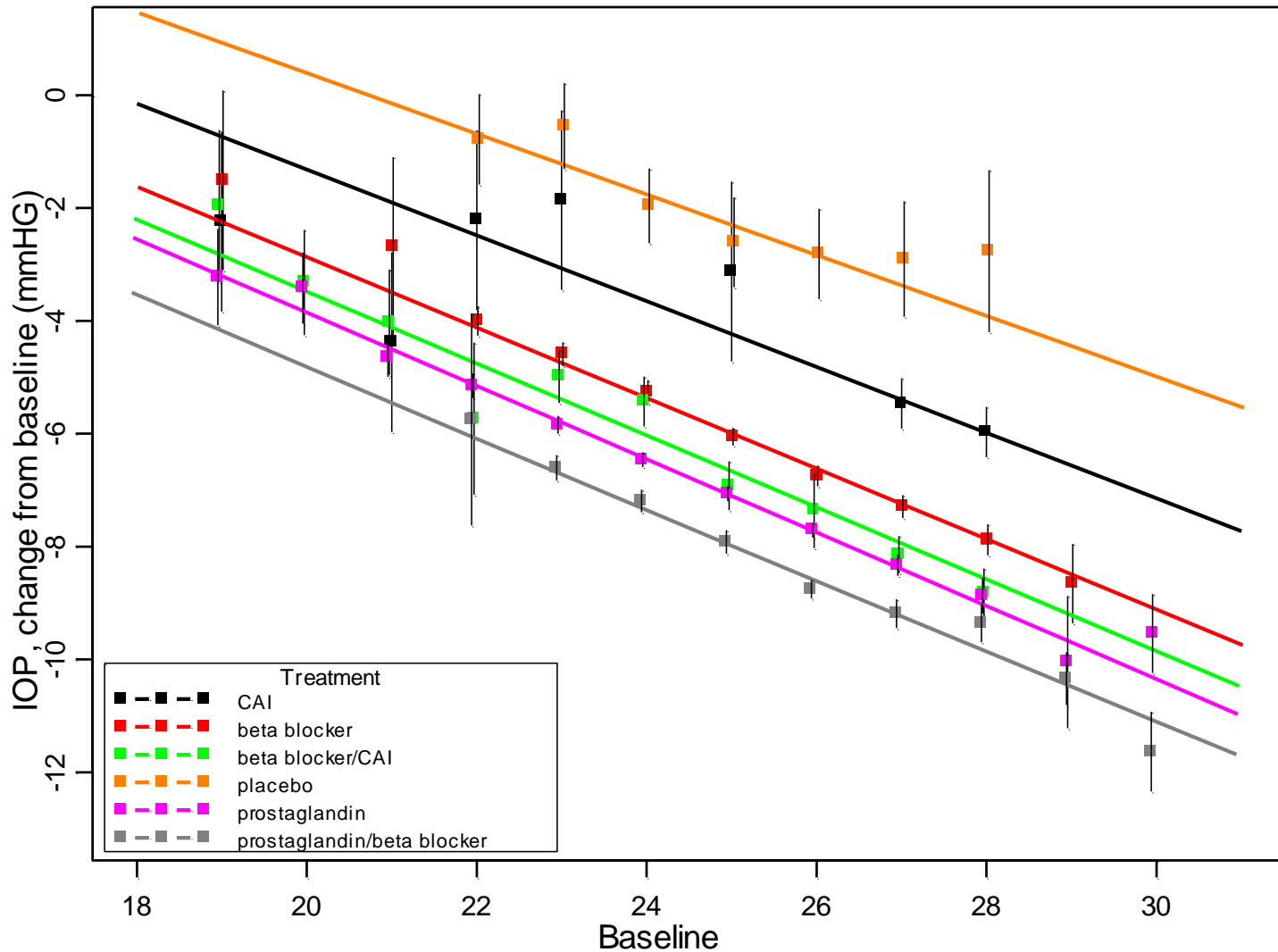
Drug	ED ₅₀ hyperemia (%) [95 CI]	ED ₅₀ IOP (%) [95 CI]	TI [95 CI]
latanoprost	0.012 [0.0066 to 0.023]	0.00096 [0.00071 to 0.0013]	13.0 [6.5 to 26.1]
bimatoprost	0.010 [0.0050 to 0.023]	0.0018 [0.00090 to 0.0035]	5.9 [2.2 to 16.2]
travoprost	0.0016 [0.00081 to 0.0031]	0.00050 [0.00038 to 0.00066]	3.1 [1.5 to 6.5]

- For drugs with the same E_{max} , the ratio of the ED₅₀ for safety and efficacy is a good measure to compare their therapeutic index (TI)
- Latanoprost provides the widest safety margin of the prostaglandin analogues

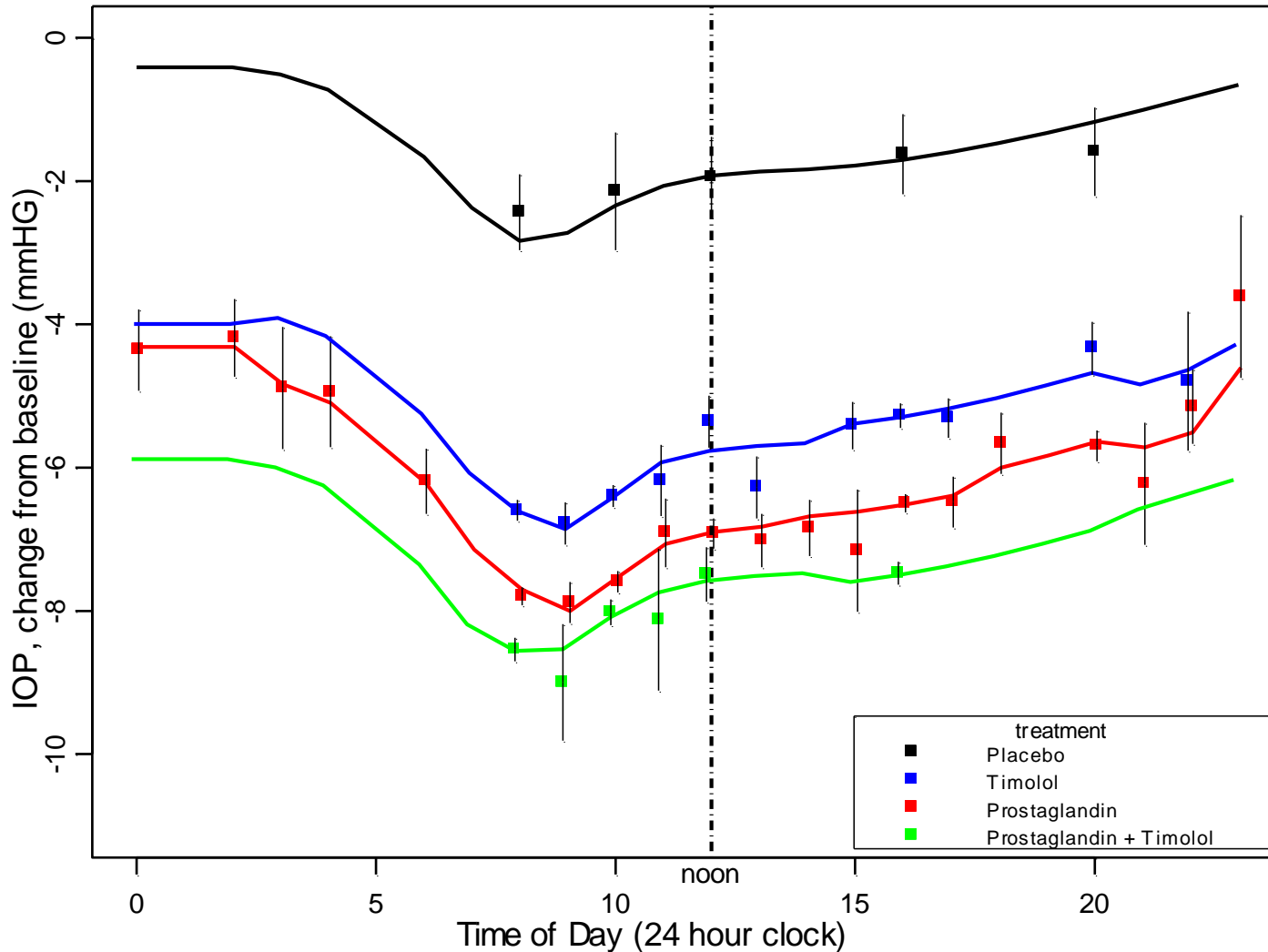
The meta-analysis provided an efficient mechanism to evaluate a novel treatment option after a phase II dose finding study



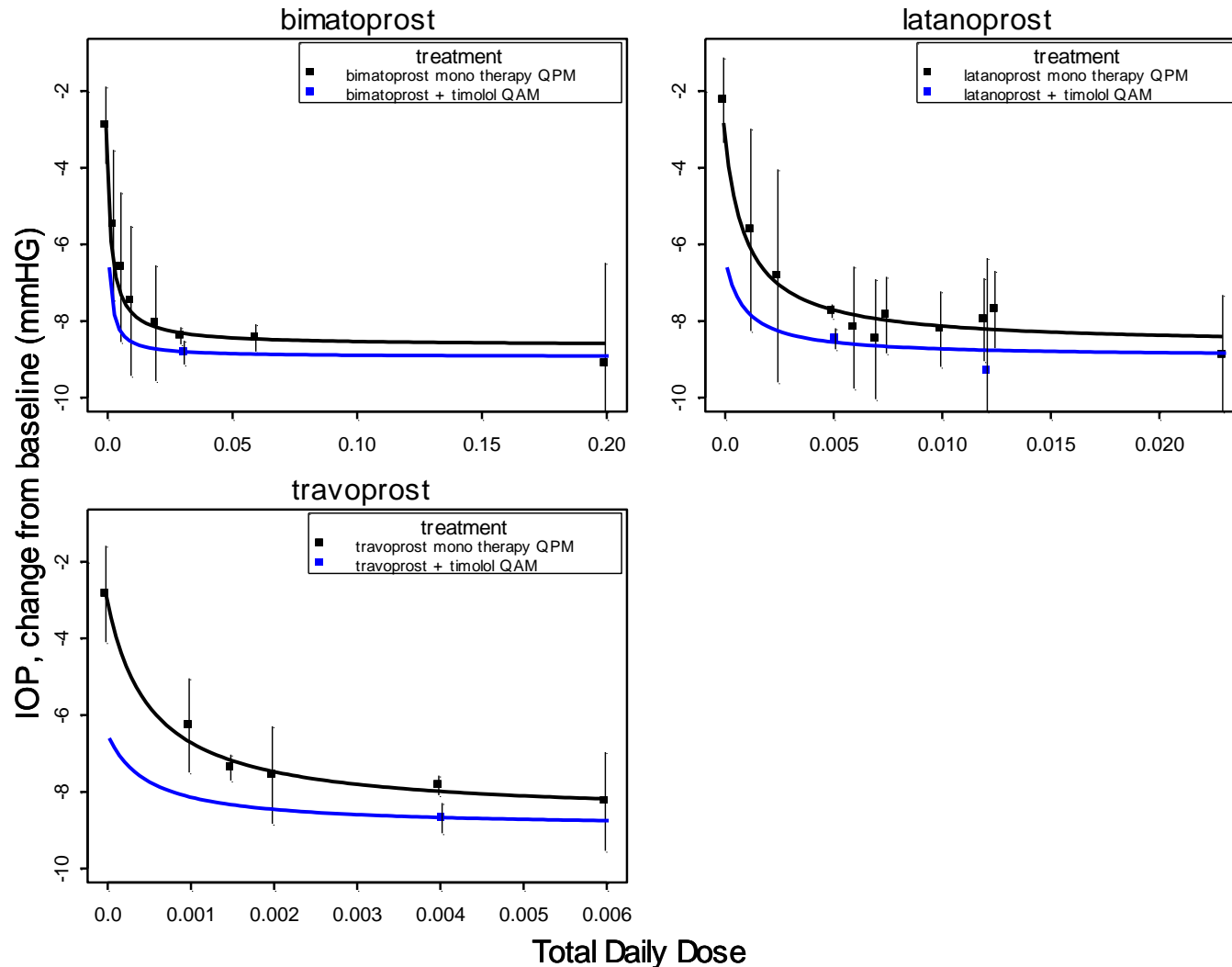
The model allowed to normalize for the impact of baseline difference across trials on the treatment effect



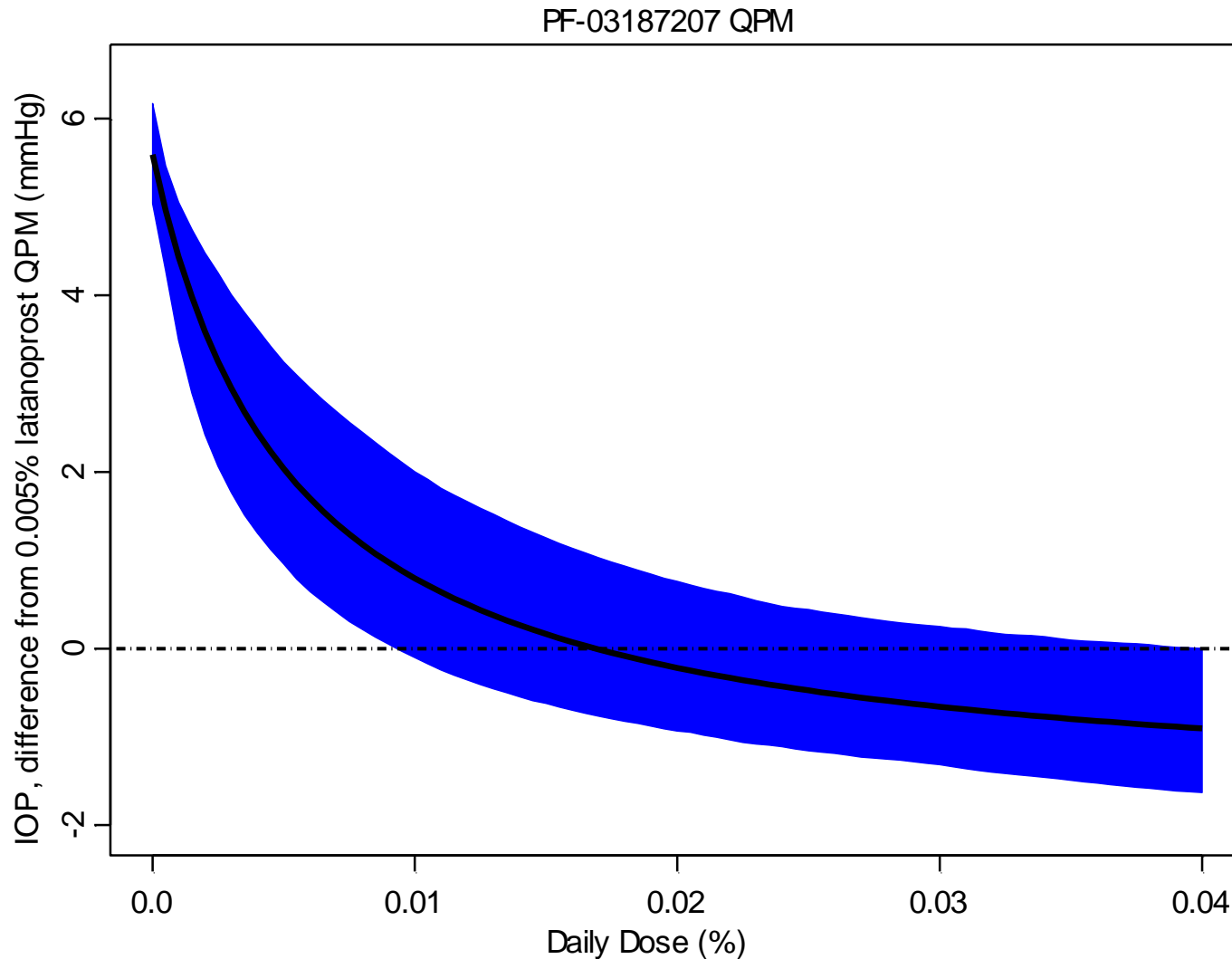
The baseline differences explain most of the variation in IOP response during a day



There was a significant (synergistic) interaction between prostaglandins and timolol, but the combined effect is not simply the sum of each effect



The meta-analysis provided an efficient mechanism to evaluate a novel treatment option after a phase II dose finding study



Summary Glaucoma

- Quantified risk/benefit of prostaglandin analogues
- Quantified risk/benefit of novel compound to SOC to facilitate dose selection and go-no go
- Characterized the pharmacodynamic interaction between drug classes
- Quantified the impact of between trial differences in baseline IOP
- Quantified circadian rhythm in IOP throughout the day

Model-Based meta-analysis

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 - Therapeutic Opportunity
- Increased precision in decision making by leveraging existing information
 - Similarities in DR within drug class
 - Similarities in PD drug interactions within drug class
 - Similarities in relationship across endpoints
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- Scaling to other indications
 - Similarities in relative differences across all drugs or within class
 - Lack of difference
- Scaling from biomarker to clinical endpoints
- Optimize Trial design
 - Impact of trial design features on placebo, treatment effect and variability

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