Individualizing Dosage Regimens: Learning about our patients optimally while treating them at the same time, achieving maximum precision throughout.

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Tasks to be done for each patient

• 1 – First, learn optimally about the drug
• 2 – Then, optimize the initial dosage regimen
• 3 – Then, learn about the drug in that patient optimally while you must treat him/her at the same time
• 4 – Continue learning and treating optimally throughout the course of treatment.
• 5 – There are tools for each part of this task.
Tool #1 - Nonparametric (NP-UPD) PK/PD models

- The most likely (ML) population parameter distributions, given the data, “CAN BE FOUND” in a discrete collection of support points, up to 1 point per subject.
- Each NP model parameter support point contains an estimate of each model parameter value, and of the probability of that collection of values in the population.
- No assumptions need to be made about the shape of the distributions in the population. They use UNCONSTRAINED parameter distributions (UPD).
What is the IDEAL Population Model?

• The correct **structural** PK/PD Model.
• The collection of each subject’s **exactly known** parameter values for that model.
• Therefore, **multiple discrete individual models**, one model from each subject.
• Usual continuous statistical summaries can also be obtained, but usually will **lose** info.
• NP - UPD models **best approach** this unattainable ideal.
An NP-UPD Population Model, made by Mallet
Tool # 2 - Multiple Model (MM) dosage design

Select your patient’s specific therapeutic target goal – not a window.

Use all multiple models in NP pop model (the blue slide).

Give a candidate dosage regimen to each model.

Predict future results from each model, each prediction weighted by its probability.

Compute WEIGHTED SQUARED ERROR of the predictions overall failure to hit the target.

Find the regimen having LEAST weighted squared error in target goal achievement. The most precise regimen.

It uses the entire distribution of each parameter, not just a single value summary of some assumed distribution.
Continuous IV Vanco. Predictions when regimen based on CPD parameter means is given to all support points.
Vanco, continuous IV. Predictions when MM regimen is given to all support points
Notice that...
The dose itself is a most important tool to minimize patient variability in response.
This is at least as important as having additional covariate information.
With parametric models you will never be aware of this issue, and never be able to do it.

Tool # 3 - Correct description of assay errors

Describe Assay Errors by $1/\text{variance}$, NOT CV%.

- Get estimate of SD for every TDM serum level going through the lab assay system.
- Variance = $SD^2$
- $1/\text{Variance} =$ correct Weight.
- **Assay Error Polynomial (AEP):**
  \[ SD = A_0C^0 + A_1C^1 + A_2C^2 + A_3C^3 \]
- Store it in the software.
- No need to censor low data any more
- No LLOQ! This is an illusion from using CV%.

Tool # 4 – Estimate CCr from changing SCr

\[ 0.4W(C2 - C1) = P - Cavg \times CCr \times 1440 \]
(Daily change = Production – Excretion)

- Where
  - \( P \) is daily creatinine production (see article)
  - \( C1 \) and \( C2 \) are SCr in mg/100ml,
  - \( W \) is weight (in hundreds of grams), and
  - \( CCr \) is creatinine clearance (in hundreds of ml/min).

Then adjust for 1.73 M² BSA

Estimation errors in CCr

CV of serum creatinine = ± 5%
CV of urine creatinine = ± 8%
Then if collect 24 hr urine with CV = ± 5%,
\[5^2=25\] twice = 50, plus \[8^2=64\], = 114.
\[\text{SQRT } 114 \sim 11\]

So the classical CCr has a CV = ± 11%,
or 95% conf limits of ± 22%
Estimated vs Measured CCr
Tool # 5 - MM Optimal TDM protocols

Do NOT wait, and do not get only steady state trough levels! **Start right with the very first dose!**
Consider 1 sample for each model parameter to be estimated. Use, for example, D-optimal design strategies. There is an optimal time to sample for each model parameter value, given a certain dosage regimen format. **Often, get a peak and a sample at about 1/3 the peak.**
Better, consider the new MM-optimal design, optimizing the times to maximize precision of dosing to desired target conc, or AUC, for example.

Do NOT waste money, effort, and patient care with poor designs. The TDM community can do a MUCH BETTER job here.
For a constant assay error, the greatest change in serum conc when volume of dist changes is at the true peak, not later. **Samples near the peak are most informative about Vd.**
The greatest change in serum conc from a change in the Kel is when the serum conc is 36% of the original peak value. **Samples near 1.44 half-times are most informative about Kel.**
Multiple Model Optimal Design

1 - Randomly sample a population model support point.
2 - Give it a simulated dose and some simulated observations, at a specific set of candidate sampling times, with assay noise.
3 - Get the MAP Bayesian posterior estimate.
4 – See if that MAP estimate corresponds to the original point (correct classification) or some other point (incorrect).
5 – Repeat steps 1-4 many times. See the percent of times the classification is correct.
6 – Do this for many candidate designs.
7 - Find the sampling design that minimizes the percent incorrect classification.

- Optimizing experimental design this way is fundamentally different from optimizing experimental design to estimate patient’s parameters, as in D-optimal design, etc.
Model Response Separation $r(t)$

- Model Response Separation $r(t)$ is the separation between two model responses at a given time $t$
  \[ r(t) = |\eta(t, a_1) - \eta(t, a_2)| \]

- Defines natural statistic for discriminating between two models
- Bayes Risk of mis-classification is shown in gray area

$r(t)$ = response separation

- Bayes Risk (gray area) decreases as response separation $r(t)$ increases
- Models are best discriminated by sampling at a time $t$ that maximizes $r(t)$
## Comparison Table

<table>
<thead>
<tr>
<th>Feature/Description</th>
<th>ED</th>
<th>EID</th>
<th>API</th>
<th>MMOpt</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invariant under regular <strong>linear</strong> reparametrization*</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Invariant under regular <strong>nonlinear</strong> reparametrization*</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Allows taking fewer than $p$ samples, $p = # \text{ of parameters}$</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Can handle heterogeneous model structures</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Gives known optimal solution to 2-model example*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Captures main elements of minimizing Bayes risk</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
</tbody>
</table>

* Proved in Bayard et. al., PODE 2013 [23]
Weighted MMOpt

- Introduce weights \( \{c_{ij}\} \) to specify a cost for each type of classification error
- Assign \( c_{ij} \) as the cost of mistaking truth subject \( i \) for subject \( j \) (\( j \neq i \))
- Choice of weights tailors experiment design to desired applications of interest
PK Population Model with 10 Multiple Model Points - First-Order PK Model

- First-Order Model
  \[
  \dot{x} = -K x + d \\
  \eta_i = \frac{x(t_i)}{V} \\
  y_i = \eta_i + \sigma_i n_i \\
  n_i \sim N(0,1) \\
  \sigma_i = 0.1
  \]

Dose input = 300 units for 1 hour, starting at time 0

<table>
<thead>
<tr>
<th>Model Parameters</th>
<th>#</th>
<th>K</th>
<th>V</th>
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<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>0.090088</td>
<td>113.7451</td>
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<td>2</td>
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<td>0.111611</td>
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<td>3</td>
<td>3</td>
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<tr>
<td>4</td>
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<td>0.108604</td>
<td>89.2334</td>
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<tr>
<td>5</td>
<td>5</td>
<td>0.103047</td>
<td>112.1093</td>
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<tr>
<td>6</td>
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<td>94.3847</td>
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<td>8</td>
<td>8</td>
<td>0.023174</td>
<td>111.7920</td>
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<td>9</td>
<td>9</td>
<td>0.087041</td>
<td>108.6670</td>
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<tr>
<td>10</td>
<td>10</td>
<td>0.095996</td>
<td>100.3418</td>
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</tbody>
</table>

Model Responses
  - Grid points 15 min apart
  - MMOOpt optimized over time grid
Unweighted MMOpt for PK Estimation

• Summary of optimal 1, 2 and 3 sample designs applied to PK Estimation

<table>
<thead>
<tr>
<th>Design Metric</th>
<th>Samples (hr)</th>
<th>Bayes Risk (prob)</th>
<th>99% conf (prob)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-Sample Design</td>
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<tr>
<td>B_{opt}</td>
<td>4.25</td>
<td>0.5474</td>
<td>±0.0015</td>
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<tr>
<td>M_{Mopt}</td>
<td>4.25</td>
<td>0.5474</td>
<td>±0.0015</td>
</tr>
<tr>
<td>2-Sample Design</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>M_{Mopt}</td>
<td>1 9.5</td>
<td>0.2947</td>
<td>±0.0014</td>
</tr>
<tr>
<td>E_{Dopt}</td>
<td>1 24</td>
<td>0.3272</td>
<td>±0.0014</td>
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<td>3-Sample Design</td>
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<td>M_{Mopt}</td>
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<td>0.2325</td>
<td>±0.0013</td>
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<tr>
<td>E_{Dopt}</td>
<td>1 1 24</td>
<td>0.2617</td>
<td>±0.0013</td>
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</table>

• **1 Sample Design**: MMOpt performance equals Bayesian optimal design (both have Bayes Risk of 0.5474).
• MMOpt performance improves on EDopt design for 2 and 3 sample designs
  – **2 Sample Design**: Bayes Risk of 0.29 versus 0.33
  – **3 Sample Design**: Bayes Risk of 0.23 versus 0.26
• All results are statistically significant to $p<0.0001$
Weighted MMOpt for AUC Control

- **OBJECTIVE:** Design an experiment most informative about next dose needed for patient to achieve a specified AUC of $\alpha_{des} = 40$

- In this case MMOpt weights are chosen as

\[
    c_{ij} = \left( \frac{D_j}{V_i K_i} - \alpha_{des} \right)^2
\]

  Squared AUC error incurred if $j$’th subject’s ideal dose $D_j$ is given to $i$’th subject

<table>
<thead>
<tr>
<th>#</th>
<th>Ideal Dose</th>
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<td>1</td>
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<td>2</td>
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<td>8</td>
<td>103.6267</td>
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<tr>
<td>9</td>
<td>378.3394</td>
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<tr>
<td>10</td>
<td>385.2965</td>
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<table>
<thead>
<tr>
<th></th>
<th>$j = 1$</th>
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<tr>
<td>$i = 1$</td>
<td>0</td>
<td>0.499</td>
<td>279</td>
<td>4.70</td>
<td>25.9</td>
<td>755</td>
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<td>893</td>
<td>9.47</td>
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<td>$i = 2$</td>
<td>0.482</td>
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<td>293</td>
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<td>18.6</td>
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<td>$i = 3$</td>
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<td>624</td>
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<td>342</td>
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<td>512</td>
<td>548</td>
<td>604</td>
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<td>$i = 4$</td>
<td>5.26</td>
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<td>236</td>
<td>0</td>
<td>59.0</td>
<td>716</td>
<td>32.8</td>
<td>858</td>
<td>0.921</td>
<td>0.0586</td>
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<td>$i = 5$</td>
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<td>0</td>
<td>835</td>
<td>2.66</td>
<td>962</td>
<td>52.5</td>
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<td>$i = 6$</td>
<td>771</td>
<td>8121</td>
<td>1185</td>
<td>6548</td>
<td>10846</td>
<td>0</td>
<td>9654</td>
<td>58.9</td>
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<td>6430</td>
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<td>$i = 7$</td>
<td>9.05</td>
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<td>25.1</td>
<td>2.90</td>
<td>808</td>
<td>0</td>
<td>939</td>
<td>34.2</td>
<td>27.3</td>
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<td>$i = 8$</td>
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<td>2715</td>
<td>12019</td>
<td>19147</td>
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<td>0</td>
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<td>$i = 9$</td>
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<td>218</td>
<td>0.967</td>
<td>78.4</td>
<td>699</td>
<td>47.0</td>
<td>843</td>
<td>0</td>
<td>0.541</td>
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<td>$i = 10$</td>
<td>6.51</td>
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<td>231</td>
<td>0.0594</td>
<td>63.5</td>
<td>712</td>
<td>36.1</td>
<td>855</td>
<td>0.521</td>
<td>0</td>
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</tbody>
</table>

Ideal Doses $\{D_j\}$ to achieve desired AUC of $\alpha_{des} = 40$

Matrix of Weights $\{c_{ij}\}$
Weighted MMOpt for AUC Control (Cont’d)

- Summary of optimal 1, 2 and 3 sample designs applied to AUC control

<table>
<thead>
<tr>
<th>Design Metric</th>
<th>Samples (hr)</th>
<th>1-Sample Design</th>
<th>2-Sample Design</th>
<th>3-Sample Design</th>
</tr>
</thead>
<tbody>
<tr>
<td>B_{opt} _C_{1}</td>
<td>12.5</td>
<td>3.6194</td>
<td>2.1102</td>
<td>1.6967</td>
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<td>MMOpt _C_{1}</td>
<td>14</td>
<td>3.7729</td>
<td>2.2575</td>
<td>1.9991</td>
</tr>
<tr>
<td>MMOpt</td>
<td>4.25</td>
<td>16.7924</td>
<td>2.6159</td>
<td>2.4194</td>
</tr>
</tbody>
</table>

- **1 Sample Design**: weighted MMOpt performance approximates that of the weighted Bayesian optimal design (RMS error of 3.62 versus 3.77 AUC units)
- MMOpt performance improves on EDopt design for 2 and 3 sample designs
  - **2 Sample Design**: RMS error of 2.11 versus 2.62 (units of AUC)
  - **3 Sample Design**: RMS error of 1.70 versus 2.42 (units of AUC)
- All results are statistically significant to p<0.0001
Tool # 6 - NP Bayesian adaptive control tools

Previous data = past experience = population model.

1 – Pop model is the Bayesian Prior (prior to now) – estimates probability of model parameters based on past experience.

2 - New data from patient. Recompute param distributions based on past + new.

3 - This is the Bayesian posterior – the individualized pt model.
An Initial Gentamicin Prediction based on population model prior: goal = 12 ug/ml
Getting Individualized Bayesian Models in Patients – 4 ways

1. MM Bayesian posteriors
2. MAP Bayesian Posteriors
3. Hybrid Bayesian posteriors.
4. Interacting MM (IMM) Sequential Bayesian Posteriors.
Estimates with MM posterior
Hybrid Bayesian posterior

• Start with MAP Bayesian. It reaches out, but not fully (shrinkage). Pop prior holds it back.
• Add new support points nearby, inside and mostly outside, to AUGMENT the pop model for the coming new patient data.
• Then do MM Bayesian on ALL the support points.
• Can also use for patients without a population model.
Patient on digoxin and quinidine - Hybrid Bayesian posterior plot
Patient on digoxin and quinidine - Hybrid Bayesian Posterior Joint Density
Interacting Multiple Model (IMM) Sequential Bayesian analysis.

• All other fitting methods assume **fixed** parameter values throughout the data analysis.
• IMM lets param distributions **change** with each new data point to get sequential Bayesian posterior distributions.
• IMM tracks Gent and Vanco behavior best in ICU patients.
By avoiding clearance and using Vs and Ks instead, the 2 separate issues of fluid balance and drug elimination can be managed best.
TDM up to now has been mostly for achieving general serum concentration guidelines.

- But now, what about seeing each patient as a unique individual?
- Patients vary greatly in their sensitivity to serum concentrations.
- Also, digoxin clinical effect does not correlate with serum concentrations, but with peripheral, nonserum compartment, concentrations.
Serum digoxin concentrations in nontoxic and toxic patients found by Doherty [1]. Note great overlap between therapeutic and toxic concentrations, and the fact that approximately half the patients with serum levels of 3.0 ng/ml or more were NOT toxic. Also note that the incidence of toxicity is very low for levels up to 1.0 ng/ml, moderate (though significant) for levels of 1.0 to 2.0, more above 2.0, but still only about 50% for levels of 3.0 ng/ml or greater.
Management of digoxin therapy

• **Two** compartment NP pop model.

• Clinical effect correlates with peripheral compartment concentrations, **not** with central (serum) concentrations.

• Plan regimens either for trough serum concentrations (usually 0.7 ng/ml) or peak peripheral concentrations (usually 7 ng/gm, 7 hrs after an oral dose).

• But patients with aur fib, flutter often need 9-18 ng/gm to convert and stay converted.
Fig. 1. Relationship between serum digoxin concentration and all-cause mortality in a post-hoc analysis of the DIG (Digitalis Investigative Group) trial (reproduced from Rathore et al.,[8] with permission). Note the statistically significant decrease in mortality (compared with placebo) at digoxin concentrations of 0.6–0.7 ng/mL (μg/L) and the trend toward increasing mortality at concentrations >1.0 ng/mL. These data have helped to redefine the therapeutic range of digoxin to a lower window of concentrations and may be expected to contribute to a further decline in the incidence of toxicity.
## Literature data

<table>
<thead>
<tr>
<th>Study</th>
<th>Digoxin / Placebo</th>
<th>Periph conc.</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Falk et al</td>
<td>9/18 v 8/18</td>
<td>8.0</td>
<td>NS</td>
</tr>
<tr>
<td>DAAAF</td>
<td>60/117 v 56/122</td>
<td>9.23</td>
<td>NS</td>
</tr>
<tr>
<td>Jordaens et al</td>
<td>9/19 v 8/20</td>
<td>11.25</td>
<td>NS</td>
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**Conversion to RSR**

<table>
<thead>
<tr>
<th>Study</th>
<th>Conversion (%)</th>
<th>Value</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hou et al</td>
<td>17/24 (71%)</td>
<td>9.0</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Weiner et al</td>
<td>40/47 (85%)</td>
<td>13.9</td>
<td>&lt;&lt;0.005</td>
</tr>
</tbody>
</table>

(Clinical Pharmacokinetics (DOI) 10.1007/s40262-014-0141-6)
New onset AF – SCr = 0.8,
Serum concentrations over time
New onset AF – SCr = 0.8, Peripheral concentrations over time
New onset AF – 96 F  SCr = 8, CCr = 3.7
Serum concentrations over time
New onset AF – 96 F  SCr = 8, CCr = 3.7
Peripheral concentrations over time
Problems with education in drug therapy

- No one teaches meaningful PK in med schools anywhere
- No one knows anything about dosage individualization
- Their only information comes from the drug companies
- Poor illiterate med schools!
- Poor illiterate docs!
- Poor poorly treated patients!
- Rich and richer drug companies!
- Rich and richer lawyers!
Problems with drug marketing

Comparison of the Degree of Platelet Aggregation Inhibition With Prasugrel Versus Clopidogrel and Clinical Outcomes in Patients With Unprotected Left Main Disease Treated With Everolimus-Eluting Stents

Angela Migliorini, MD, Renato Valenti, MD, Guido Parodi, MD, Rossella Marcucci, MD, Rosanna Abbate, MD, Nazario Carrabba, MD, Gian Franco Gensini, MD, and David Antoniucci, MD

148 received prasugrel. The primary end point rate was lower in the prasugrel group compared with clopidogrel group: 1.3% and 9.6%, respectively (p = 0.002). Residual platelet reactivity was less in the prasugrel group compared with clopidogrel group (adenosine diphosphate 10 μmol/L 37 ± 17% and 45 ± 15%, respectively, p < 0.001). At multivariate analysis, prasugrel treatment was related to the primary end point (hazard ratio 0.17; 95% confidence interval 0.04 to 0.77, p = 0.022). In conclusion, in patients treated with EES for ULMD, prasugrel compared with clopidogrel is associated with increased platelet aggregation inhibition and a better clinical outcome. © 2013 Elsevier Inc. All rights reserved. (Am J Cardiol 2013;112:1843–1848)
Suppressing their own science for marketing!

- They **have** the data for each patient -
- **Outcome**, **and** **Antiplatelet effect**.
- They can easily find the antiplatelet effect associated with best outcome, least bleeding.
- They can set a **target antiplatelet effect**, **and**
- **dose** each patient to achieve it!
- Why do they **advertise** that this is **NOT NEEDED??** Why?? Think about it!
- **WE BADLY NEED INDIVIDUALIZED DOSAGE.**