celerion

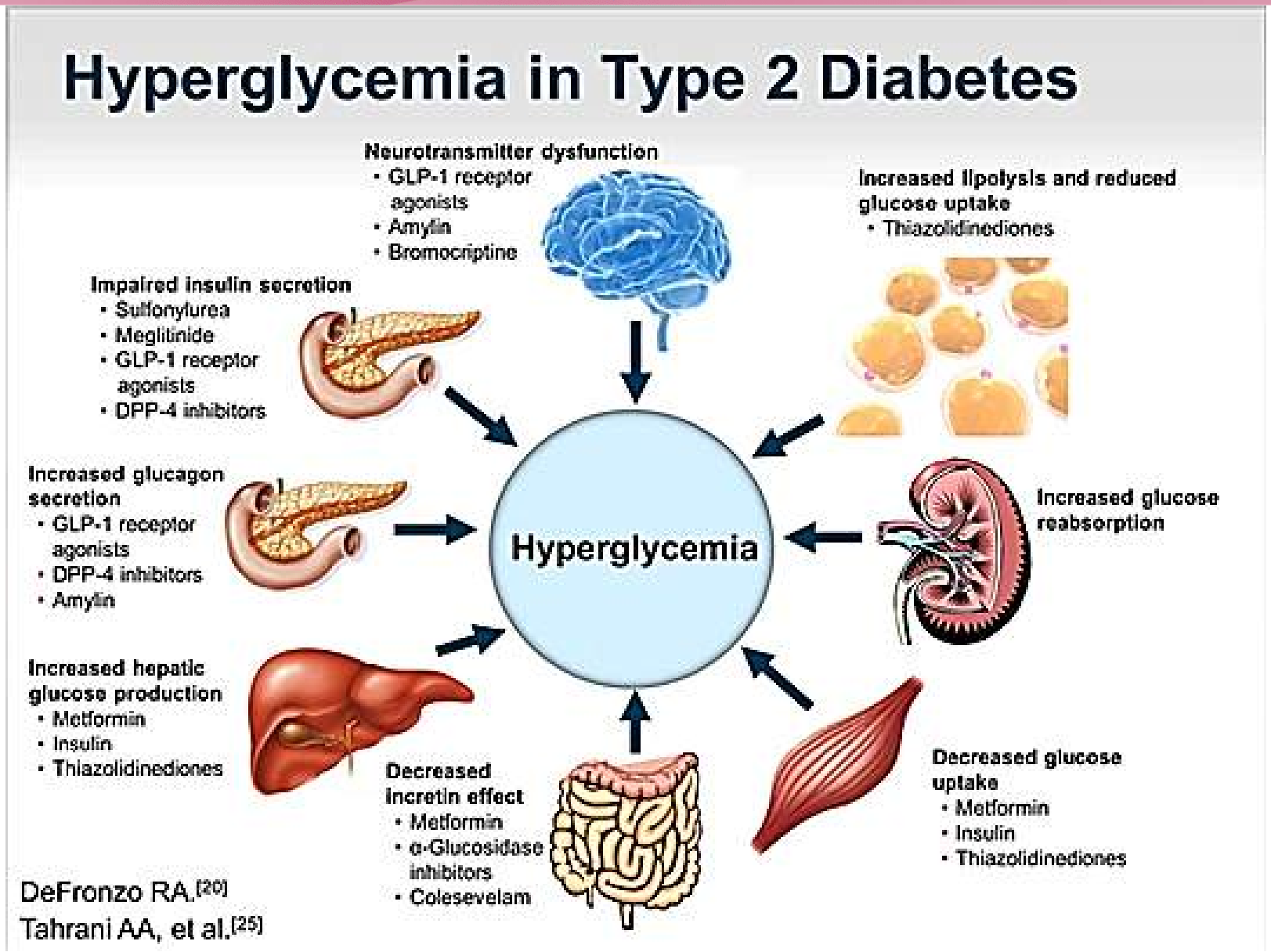
Applied Translational Medicine

Optimizing Early Phase Antidiabetic Drug Development

Clayton A. Dehn, M.S.

Executive Director, Metabolic Diseases

The Ominous Octet: Pathologies,Therapies and Targets

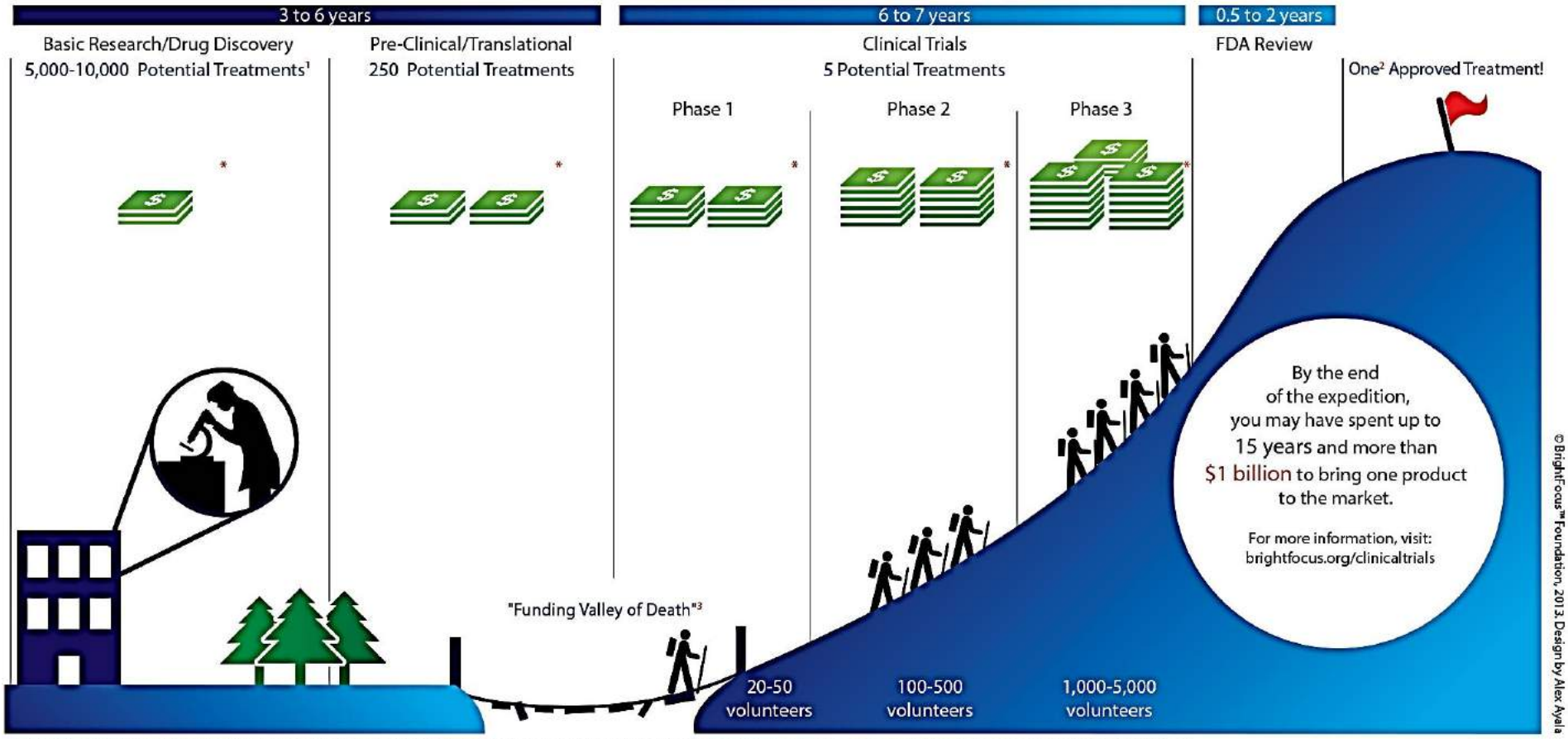


An Uphill Battle

Imagine leading an expedition where every step is more difficult than the last...

The long journey begins in the lab, where scientists spend years testing thousands of ideas. Next, crossing the so-called "Funding Valley of Death" requires the resources and time needed to complete clinical trials, testing safety and effectiveness among what could end up being thousands of volunteers. At the end of this steep financial and scientific climb: Food and Drug Administration approval for a new treatment. Ultimately, it may have taken up to 15 years and more than $1 billion to bring this treatment to the market.

BrightFocus™ Foundation
Cure in Mind. Cure in Sight.



1 Although we are using the word "treatment," clinical trials also involve medical research studies in which people participate as volunteers to test new methods of prevention, screening, and diagnosis of disease.

2 After approval, the product is manufactured for sale on the market, and the process enters Phase 4 (Post-Marketing Monitoring/Clinical Trials). At this point, the FDA monitors for public safety and adverse events, and the sponsor company may begin Phase 4 Clinical Trials to obtain information about long-term effects or to test the product in special patient populations.

3 The "Funding Valley of Death" is the financial challenge many promising treatments face in having the opportunity to be scientifically tested in a clinical trial. In many cases, further financial support or partnerships are necessary to proceed.

* The cost of bringing a drug to market depends on a number of variables, but could be more than $1 billion, including approximately $50-840 million for Basic Research/Drug Development and Pre-Clinical/Translational research, and approximately $50-970 million to complete all three Phases of the Clinical Trials.

Cardiovascular Risk Assessment

In order to satisfy the initial approvability hazard ratio requirements of 1.8 to 1.3, drug development programs should target between approximately 120 to 700 CV events respectively. This will require studying between 4,500 and 15,000 T2DM patients.

Adds at least a year to the drug development process and an estimated **250 to 500 million** US Dollars to the cost of developing a new diabetes medication.

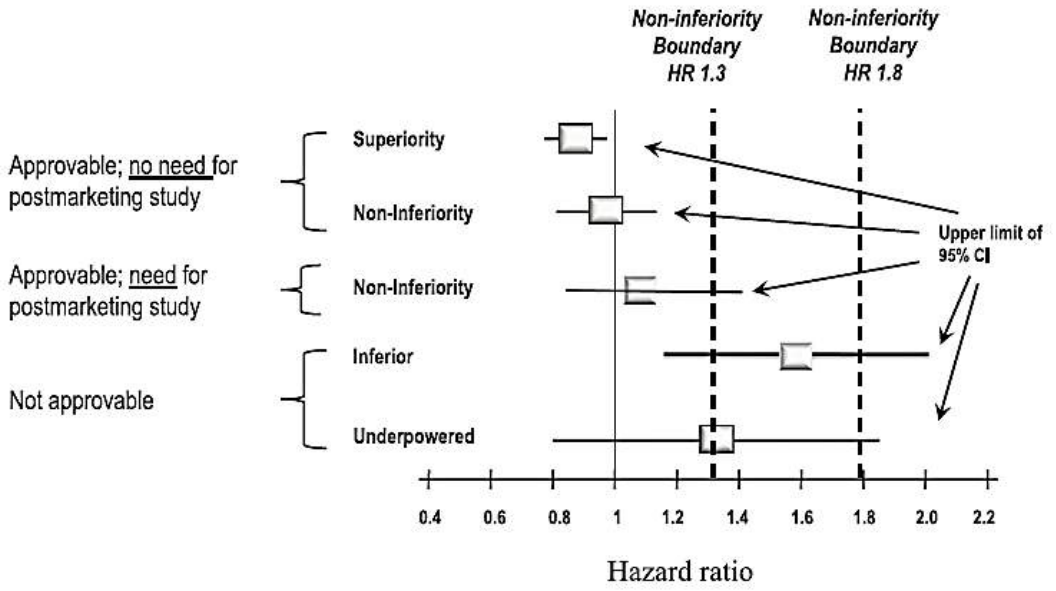
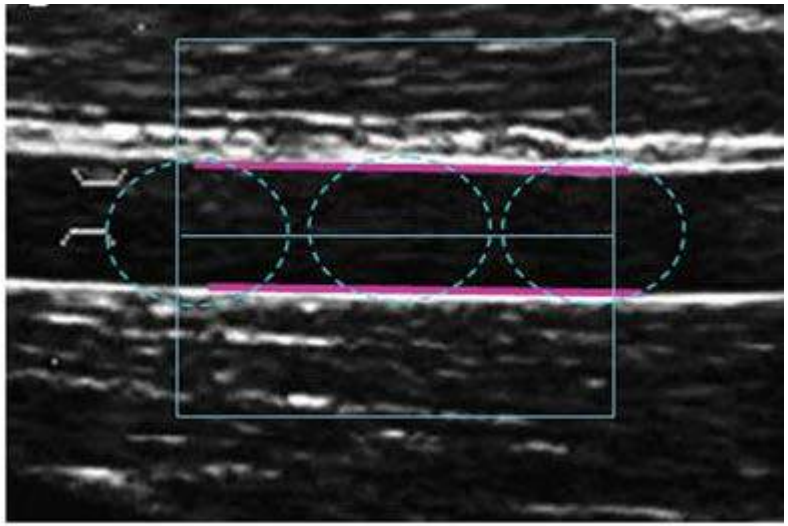


Figure 1—*FDA CV safety: CI bars. The FDA guidelines provide statistical hurdles for approval. Five hypothetical examples of possible hazard ratios and the upper limit of the 95% CI of a development plan are shown as well as the regulatory consequences of each outcome.*

Boaz Hirshberg, Arie Katz. "Cardiovascular Outcome Studies With Novel Antidiabetes Agents: Scientific and Operational Considerations" *Diabetes Care* 36.2 (2013): S253-S258.

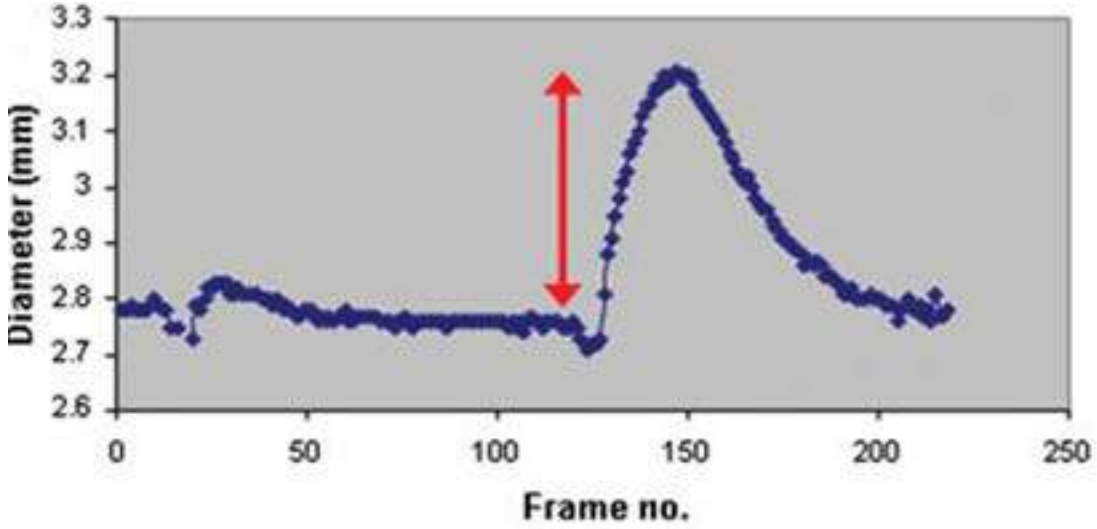
David a. Fryburg, and Maria T. Vassileva. "Atherosclerosis Drug Development in Jeopardy: The need for Predictive Biomarkers of Treatment Response" *Science Translational Medicine* 3.72 (2011): 1-5.

FMD as an Early Signal of CV Risk



Non-Invasive, ultrasonographic measure of nitric oxide cascade mediated vascular dilation of the diameter of the brachial artery in response to hyperemia induced by short-term occlusion of the forearm.

The FMD response is sensitive to even short term interventions and is highly correlated to cardiovascular outcomes.



Marietta Charakida, Stefano Masi, Thomal f. Luscher, John J.P. Kastelein, and John E. Deanfield. "Assessment of Atherosclerosis: the rol eof flow-mediated dilatation" *European Heart Journal* 31 (2010): 2854-2861.

FMD as an Early Signal of CV Risk

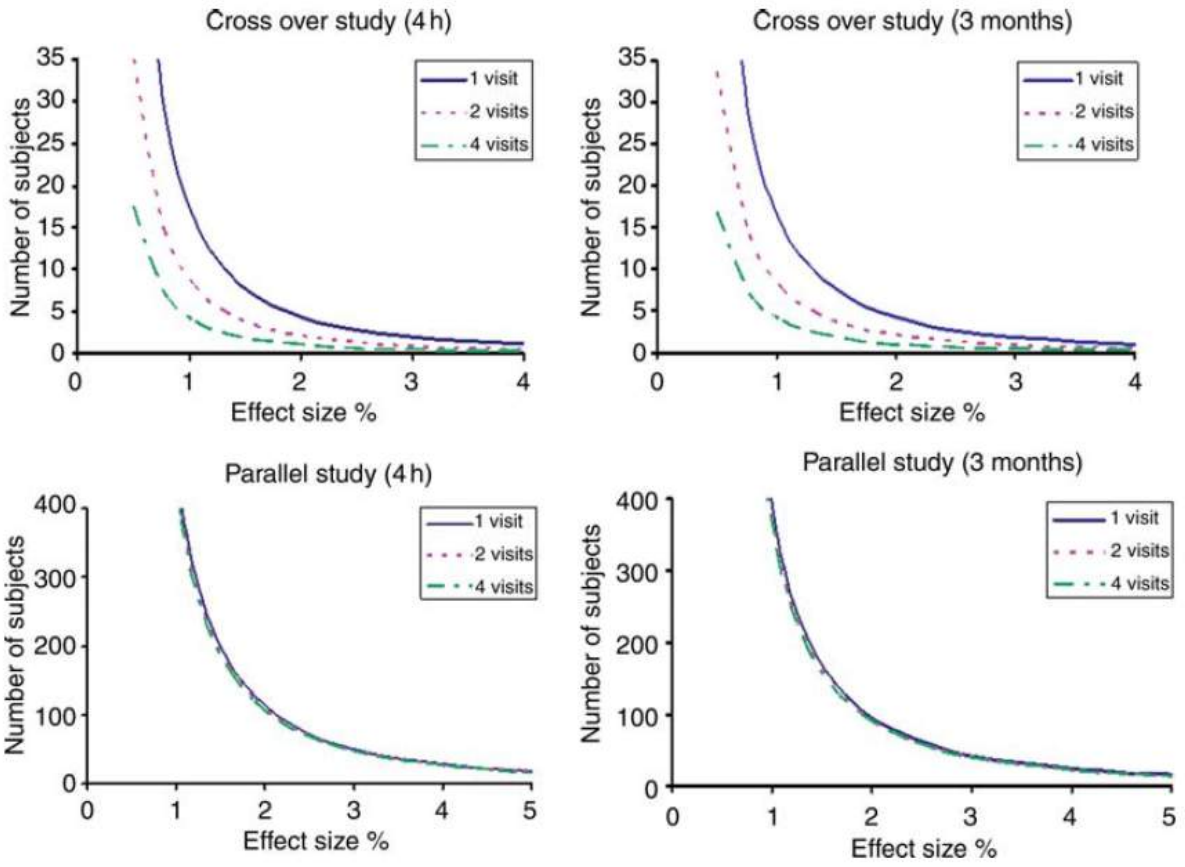
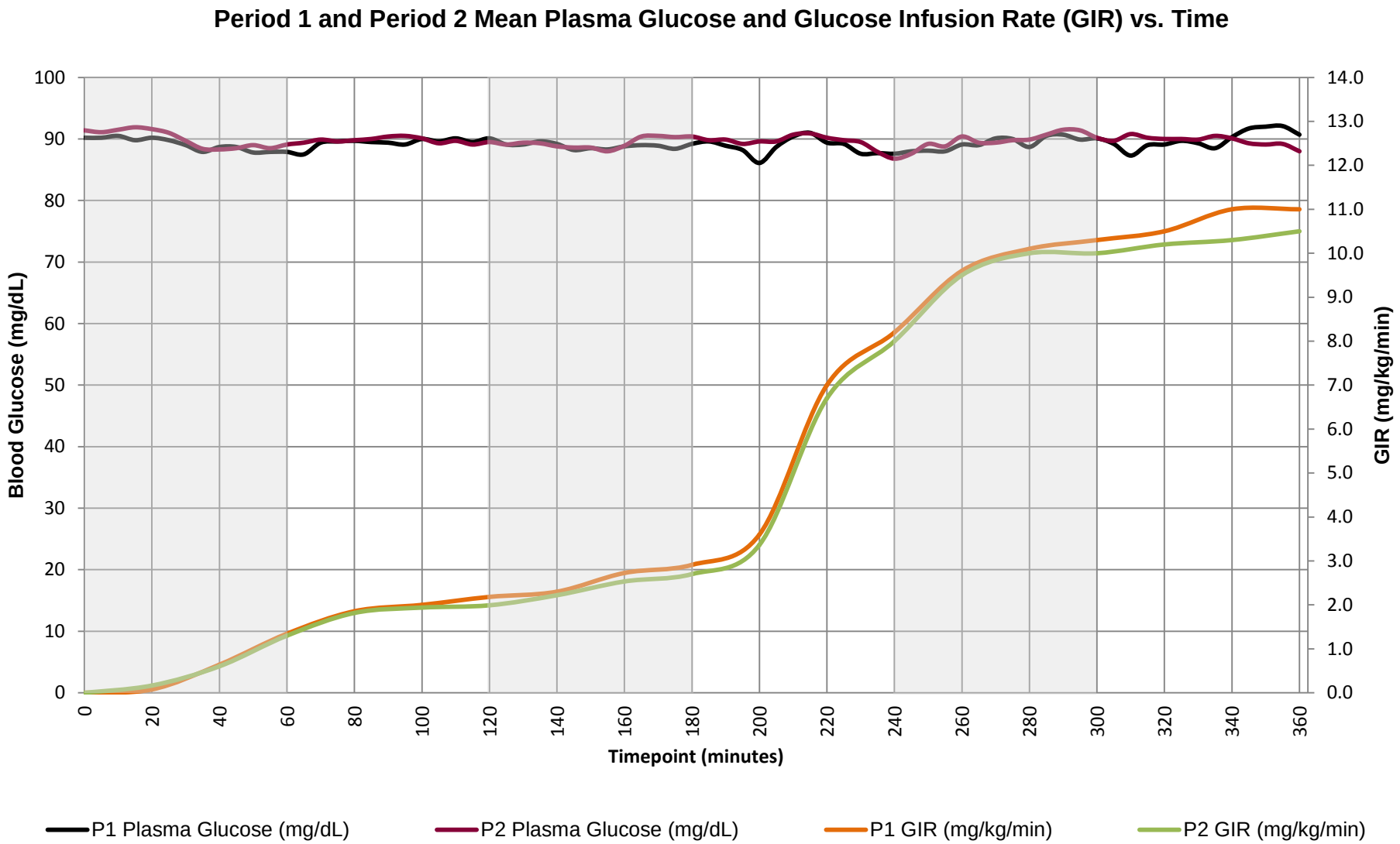


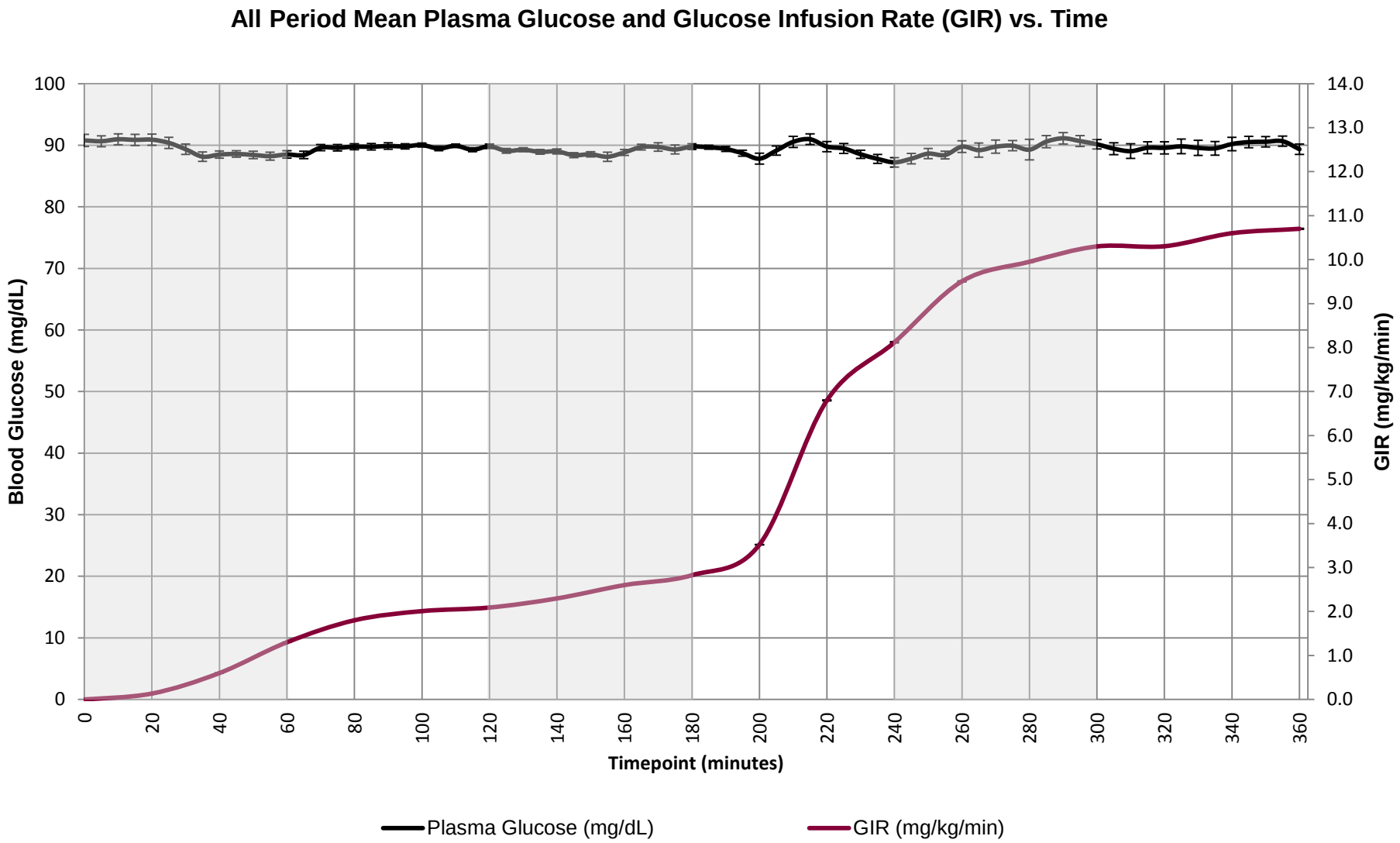
Figure 2 Power curves for estimating subjects required for flow-mediated dilatation studies in crossover and parallel studies. Relation between effect on maximum percent change in flow-mediated dilation (%) and number of subjects required in crossover and parallel study designs at 80% power and 5% significance, 4–6 h and 3 months apart with three monitoring strategies: 1, 2, or 4 measures pre- and post-treatment.

Marietta Charakida, Stefano Masi, Thomal f. Luscher, John J.P. Kastelein, and John E. Deanfield. "Assessment of Atherosclerosis: the rol eof flow-mediated dilatation" *European Heart Journal* 31 (2010): 2854-2861.

Repeatability of the Hyperinsulinemic-Euglycemic Glucose Clamp



Repeatability of the Hyperinsulinemic-Euglycemic Glucose Clamp



Additional Testing Methods

- **Glycemic Control or Metabolic Regulation**
  - 24hr glucose
  - Continuous Glucose Monitoring
  - Oral Glucose Tolerance Tests (OGTT)
  - Meal Tolerance Tests (MTT)
  - Intravenous Glucose Tolerance Tests (IVGTT)
  - Pancreatic Maximum Stimulation Tests
  - Graded Glucose Infusions (GGI)
  - Glucose Clamping
  - Isotope Dilution Methods
    - Stable and radioactive isotopes
- **Satiety**
  - Visual Analog Scales (VAS)
  - Food intake models
- **Cardiometabolic Endothelial Function Testing**
  - Flow Mediated Dilation (FMD)
- **Substrate Utilization and Energy Expenditure**
  - Indirect Calorimetry
- **Metabolically Relevant Medical Imaging** (DEXA, MRI)
- **Metabolically Relevant Biopsies** (Adipose, Muscle)

celerion

Risks Deferred are Risks Accepted

celerion

Applied Translational Medicine

Questions?