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Applied Translational Medicine

Celerion's Symposia Series: Bridging the Gap from Phase I to Proof-of-Concept

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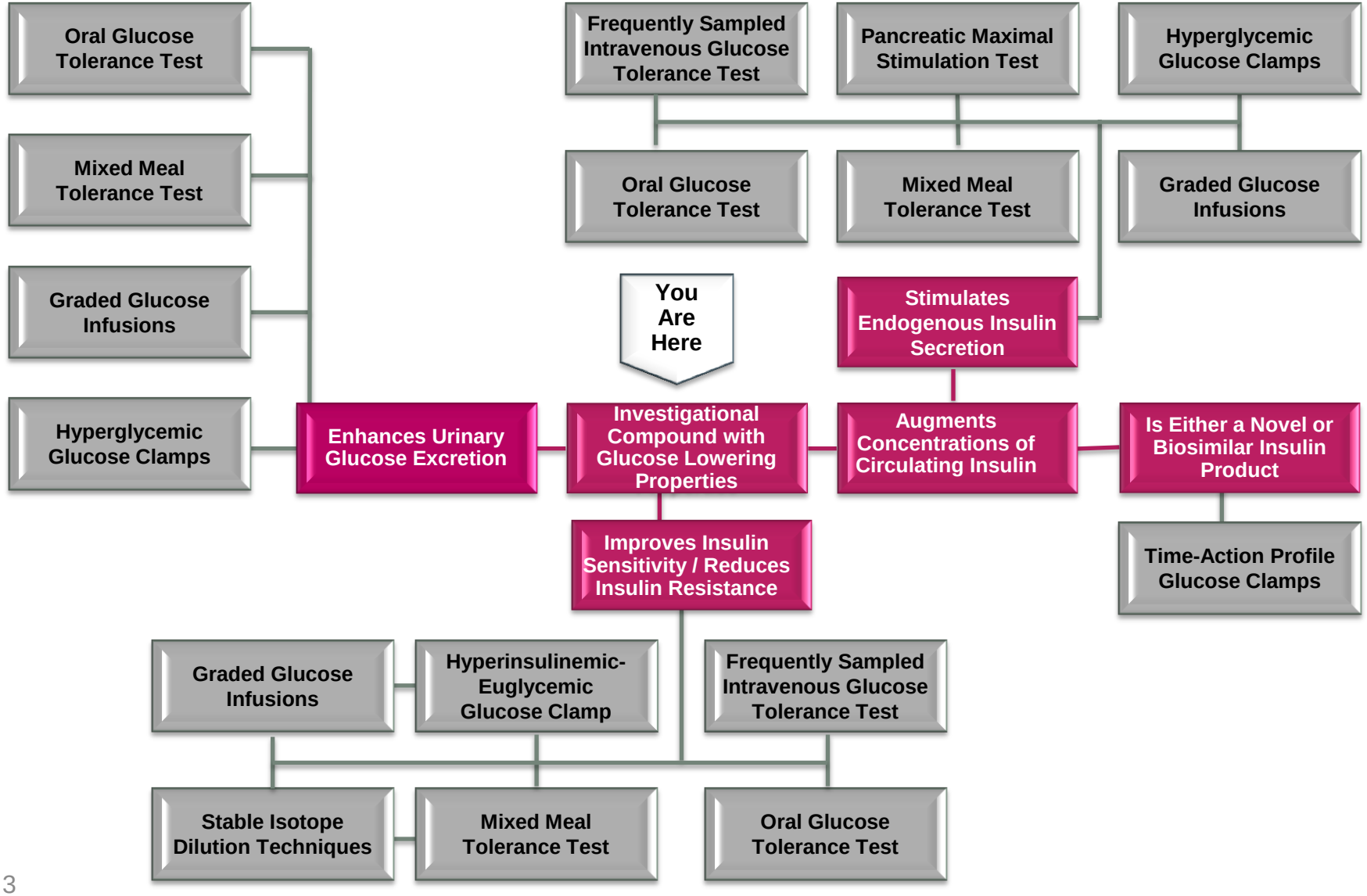
Early Phase Clinical Research Signals of Efficacy in Developing Therapies for Diabetes, Obesity, and Metabolic Disorders

Clayton Dehn MS

Executive Director, Metabolic Diseases

Navigating Your Way to Early Signals of Efficacy



Beta Cell Function Testing

Table 2.1 Summary of Tests' Characteristics

test	β-cell function characteristics tested	specific equipment	insulin sensitivity[1]	C-peptide[2]	complexity[3]
IVGTT	first phase; empirical second phase indices; some index of the β-cell dose-response by modeling	infusion pump[4], modeling software[5]	yes	optional	+++[6]
Hyperglycaemic clamp	first and second phase indices	infusion pump, glucose analyser for bedside measurement	yes	optional	++++
Graded glucose infusion test	β-cell dose-response	infusion pump	no	necessary	+++++
Arginine, basic	'maximal' insulin response		no	optional	++
Arginine, glucose potentiation	'maximal' insulin response, potentiation of the insulin response with exposure to hyperglycaemia	infusion pump	no	optional	+++++
OGTT + empirical indices	empirical β-cell function indices (typically the insulinogenic index); surrogate first and second phase indices		yes	optional	++
OGTT + modeling	first phase marker, β-cell dose-response, potentiation parameters	modeling software	yes	necessary	+++
HOMA	empirical β-cell function index		yes	optional	+

1. See Chapter 3 for a discussion of the indices.
2. Tests requiring C-peptide also require software for deconvolution. C-peptide deconvolution can be used with all tests.
3. Complexity ranking is somewhat subjective (+ = simplest; +++++ = most complex).
4. The infusion pump is used for insulin infusion in insulin-modified IVGTT.
5. Modeling software to calculate additional β-cell function indices is optional.
6. The IVGTT complexity depends remarkably on the specific protocol used and on the data analysis procedures.

Roden, Michael. Ed. *Clinical Diabetes Research Methods and Techniques*. West Sussex: John Wiley & Sons. 2007.

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Beta Cell Function Testing

Table 2.2 Practical Considerations

- Select test considering:
  - Desired β-cell function indices;
  - Test complexity;
  - Availability of laboratory equipment and software for data analysis;
  - Possibility of also assessing insulin sensitivity.
- Use intravenous standardised tests if appropriate normalisation to glucose levels is difficult.
- Keep in mind that very simplified tests have limited reliability.
- Verify on the original references the protocol details, dosages and sampling schedule before planning experiments. Strict observance of the protocol is important for test quality.
- Use reliable insulin (and C-peptide) assays and perform measurements accurately.
- Use C-peptide to calculate insulin secretion by deconvolution when possible.
- If the test is used to compare groups, be sure that tests yield results that are comparable. For instance, hyperglycaemic clamps at different glucose levels are not comparable.
- Keep in mind that β-cell function may depend on insulin resistance. For instance, first phase secretion indices from the IVGTT cannot be compared if insulin sensitivity is different.
- Use caution with indices that express β-cell function in relation to insulin sensitivity (in particular with the disposition index). The assumptions under which these indices are valid must be verified.

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Insulin Sensitivity Testing

Table 3.1 Summary of Tests' Characteristics

test	characteristics of the insulin sensitivity index	specific equipment/ pharmacological agents	β-cell function[1]	complexity[2]
HOMA	empirical index of fasting (liver) insulin resistance		yes	+
QUICKI	empirical index of fasting (liver) insulin sensitivity			+
Euglycemic clamp[3]	estimate of glucose uptake at fixed insulin levels	infusion pumps, glucose analyser for quick bedside measurement	no	++++
Hyperglycaemic clamp[3]	estimate of ratio of glucose uptake to prevailing insulin levels	infusion pumps, glucose analyser for quick bedside measurement	yes	++++
IST	estimate of glucose uptake at fixed insulin levels	infusion pumps/somatostatin	no	++++
IVGTT	estimate of fractional glucose clearance (mostly skeletal muscles and adipose tissues) normalised to insulin	infusion pump[4]; modeling software	yes	+++
OGTT	surrogate estimates of clamp insulin sensitivity	spreadsheet	yes	++
ITT	rate of glucose disappearance		no	+++

1. See Chapter 2 for a discussion of the indices.
2. Complexity ranking is somewhat subjective (+ = simplest; ++++ = most complex).
3. See Chapter 4 for use, outcomes and limitations of these tests.
4. The infusion pump is used for insulin infusion in insulin-modified FSIGT.

Roden, Michael. Ed. *Clinical Diabetes Research Methods and Techniques*. West Sussex: John Wiley & Sons. 2007.

Insulin Sensitivity Testing

Table 3.2 Practical Considerations

- Select test considering:
  - The reliability of the insulin sensitivity indices in the specific context of the study;
  - Test complexity;
  - Availability of laboratory equipment and software for data analysis;
  - Possibility of also assessing beta-cell function
- If the assessment of insulin sensitivity is critical for the study, the direct tests (1st choice: glucose clamp; 2nd choice: IVGTT) must be used.
- Keep in mind that very simplified tests have limited reliability.
- Verify on the original references the protocol details: check especially the doses of given substances and the sampling schedules before planning experiments. Strict observance of the protocol is important for test quality and reliability of results.
- Use the appropriate insulin dose with the insulin-modified-FSIGT.
- If the test is used to compare groups, be sure that tests yield results that are comparable. For instance, OGTT and FSIGT are not comparable.

Roden, Michael. Ed. *Clinical Diabetes Research Methods and Techniques*. West Sussex: John Wiley & Sons. 2007.

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Cardiovascular Risk Assessment

- In 2008 the FDA Endocrinologic and Metabolic Advisory Committee determined that concerns about CV risk should be more thoroughly addressed during drug development.

US Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation and Research (2008). *Guidance for Industry: Diabetes Mellitus – Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes*.

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Cardiovascular Risk Assessment

- Must include patients with advanced disease, elderly, and renally impaired patients
- A minimum of two years of CV safety data must be provided
- All Phase II and III data should include a prospective adjudication of CV events including
  - Typically Major Adverse Cardiac Events (MACE):
    - CV mortality
    - MI
    - Stroke
  - May also include:
    - Hospitalization for Acute Coronary Syndrome
    - Urgent revascularization
    - Other end points

Boaz Hirshberg, Itamar Raz. "Impact of the U.S. Food and Drug Administration Cardiovascular Assessment Requirements on the Development of Novel Antidiabetes Drugs" *Diabetes Care* 34.2 (2011): S101-S106.

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Cardiovascular Risk Assessment

- To satisfy these statistical guidelines, the analysis of CV events may include meta-analysis of all:
  - Placebo-controlled studies
  - Placebo or IP add on (to standard therapy) studies
  - Active-Controlled studies
  - Or an additional single, large safety study that alone or in combination with other studies satisfy these guidelines

Boaz Hirshberg, Itamar Raz. "Impact of the U.S. Food and Drug Administration Cardiovascular Assessment Requirements on the Development of Novel Antidiabetes Drugs" *Diabetes Care* 34.2 (2011): S101-S106.

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Cardiovascular Risk Assessment

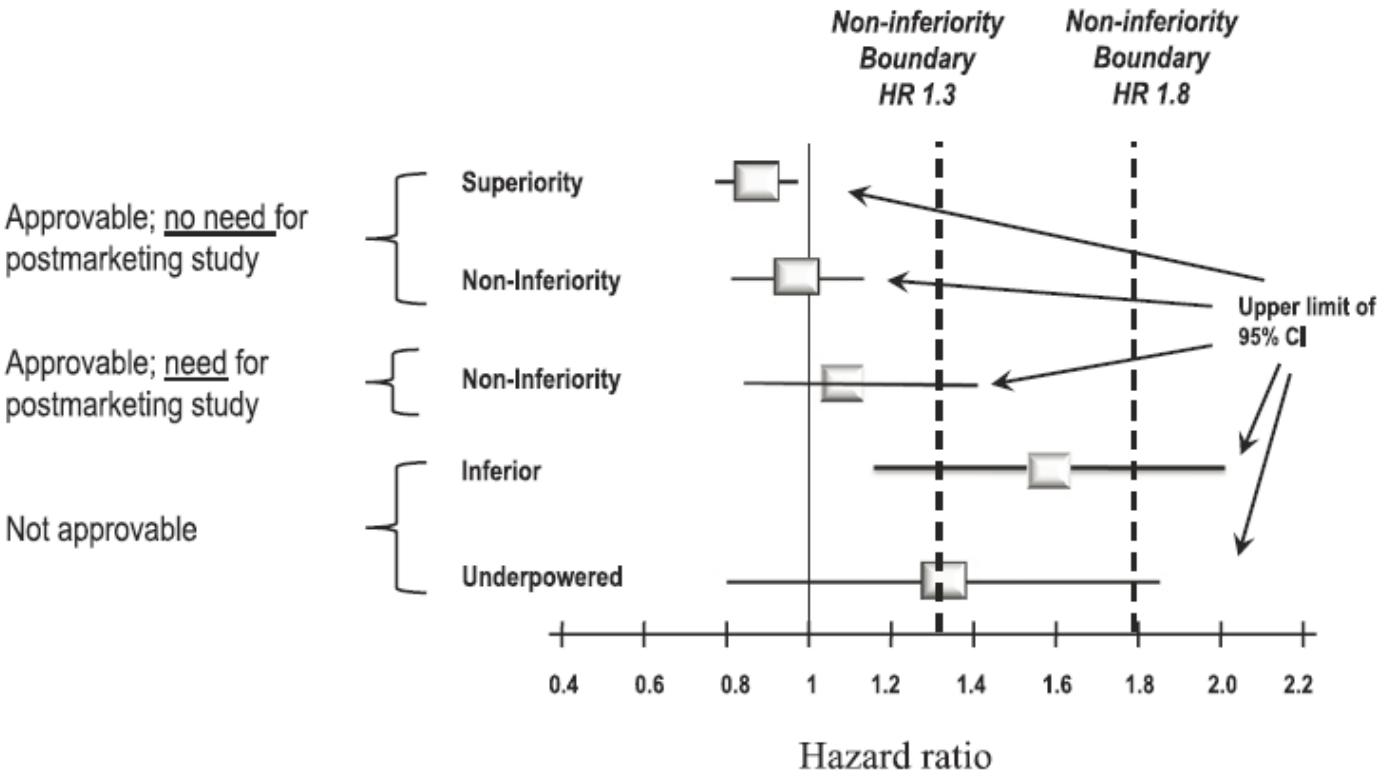

Figure 1—*FDA CV safety: CI bars. The FDA guidelines provide statistical hurdles for approval. Five hypothetical examples of possible hazard ratios and the upper limit of the 95% CI of a development plan are shown as well as the regulatory consequences of each outcome.*

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

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Cardiovascular Risk Assessment

- Assuming a novel antidiabetic drug is CV risk neutral
  - 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 translates into an expected recruitment goals of between 4,500 and 15,000 patients into the CV outcomes studies

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

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Cardiovascular Risk Assessment

- Satisfying the required antidiabetic drug development CV risk assessment adds at least a year to the drug development process and an estimated

  250 to 345 million US Dollars!!

- "Very few pharmaceutical companies have the resources, expertise, and financial capability to conduct such studies and it may no longer be feasible for small biotech and pharmaceutical companies to independently develop and launch antidiabetes medications."

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.

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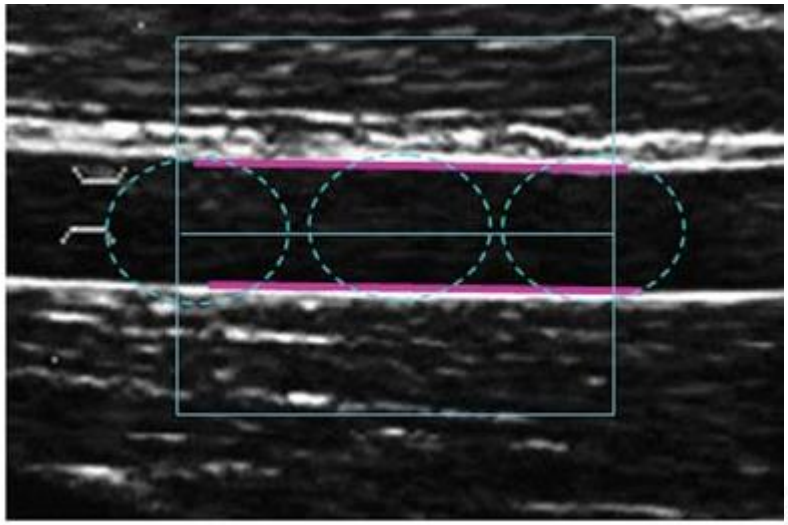
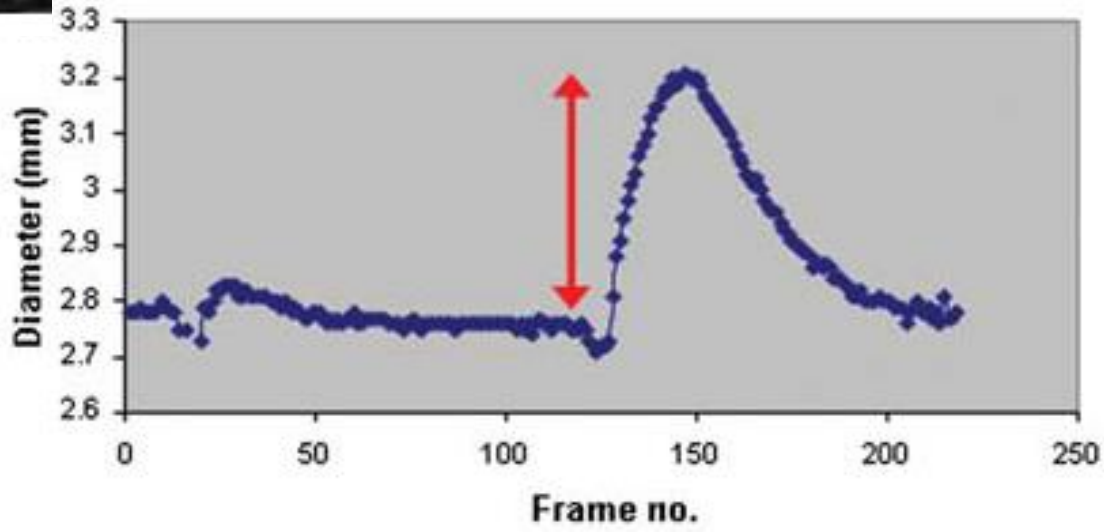
FMD as an Early Signal of CV Risk





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 Power Curves

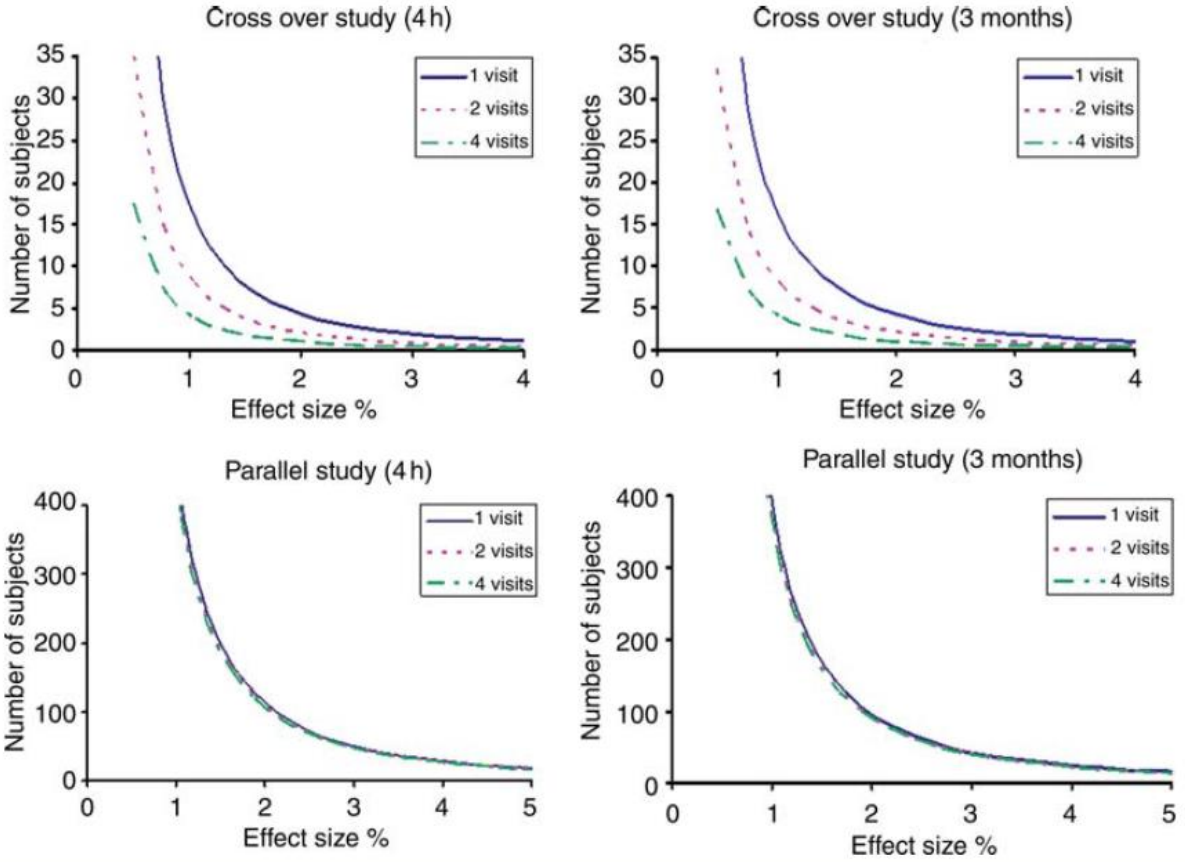


Figure 2 Power curves for estimating subjects required for flow-mediated dilatation studies in crossover and parallel studies. Relation between effect on maximum percent change in flow-mediated dilation (%) and number of subjects required in crossover and parallel study designs at 80% power and 5% significance, 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.

FMD example

- Results of FMD endothelial function testing
  - 24 normal healthy male participants
  - Age: 25.7 ± 6.5 years
  - BMI: 22.8 ± 1.3 kg/m^2
  - Fasting glucose: 4.7 ± 0.4 mmol/L
  - Three-Period Crossover in Random Order
    - Treatments: A, B, C
  - Endpoints
    - Peak Glucose 0-180 minutes
    - Glycemic Excursion 0-180 minutes
    - FMD Endothelial Function Testing at 45 minutes

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FMD Example

Glycemic Profile		
Treatment	Peak Glucose (mmol/L)	$AUC_{0\text{-}180}$ Glucose Excursion
A	10.1 ± 2.7	1247 ± 364.8
B	8.1 ± 1.5	1058.6 ± 148
C	6.7 ± 0.8	947.9 ± 151.7

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FMD Example

- Results of FMD endothelial function testing
  - Baseline FMD similar across all three treatments
  - Change from baseline
    - A: + 11%; No significant change from baseline p=ns
    - B: -17%; No significant change from baseline p=ns
    - C: -76%; $p<0.01$
  - Treatment C resulted in significantly more blunting versus A or B ($p<0.05$ for both)

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FMD Example

- Review of financial impact of glycemic and FMD testing in early phase
  - Abandon treatment A for inferior glycemic control in spite of neutral cardiovascular risk assessment
  - Progress treatment B for superior glycemic control and neutral results from cardiovascular risk assessment
  - Abandon treatment C in spite of superior glycemic control due to inferior of cardiovascular risk assessment
  - Estimated cost of adding FMD as an early signal of cardiovascular risk to this study
    - Approximately $110,000

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Questions?