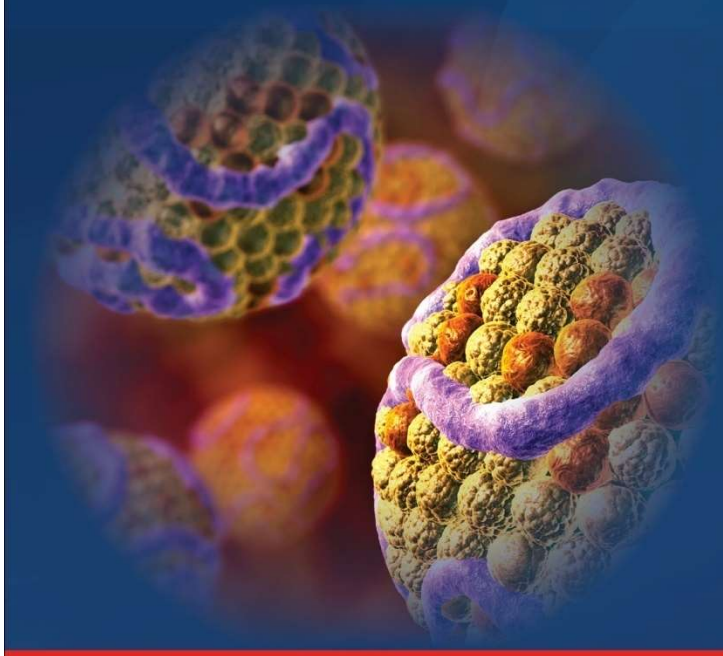


Innovation in Clinical Trials to Meet Increased Patient, Provider and Payer Demands for Safe, Effective and Cost-Effective Personalized Therapies

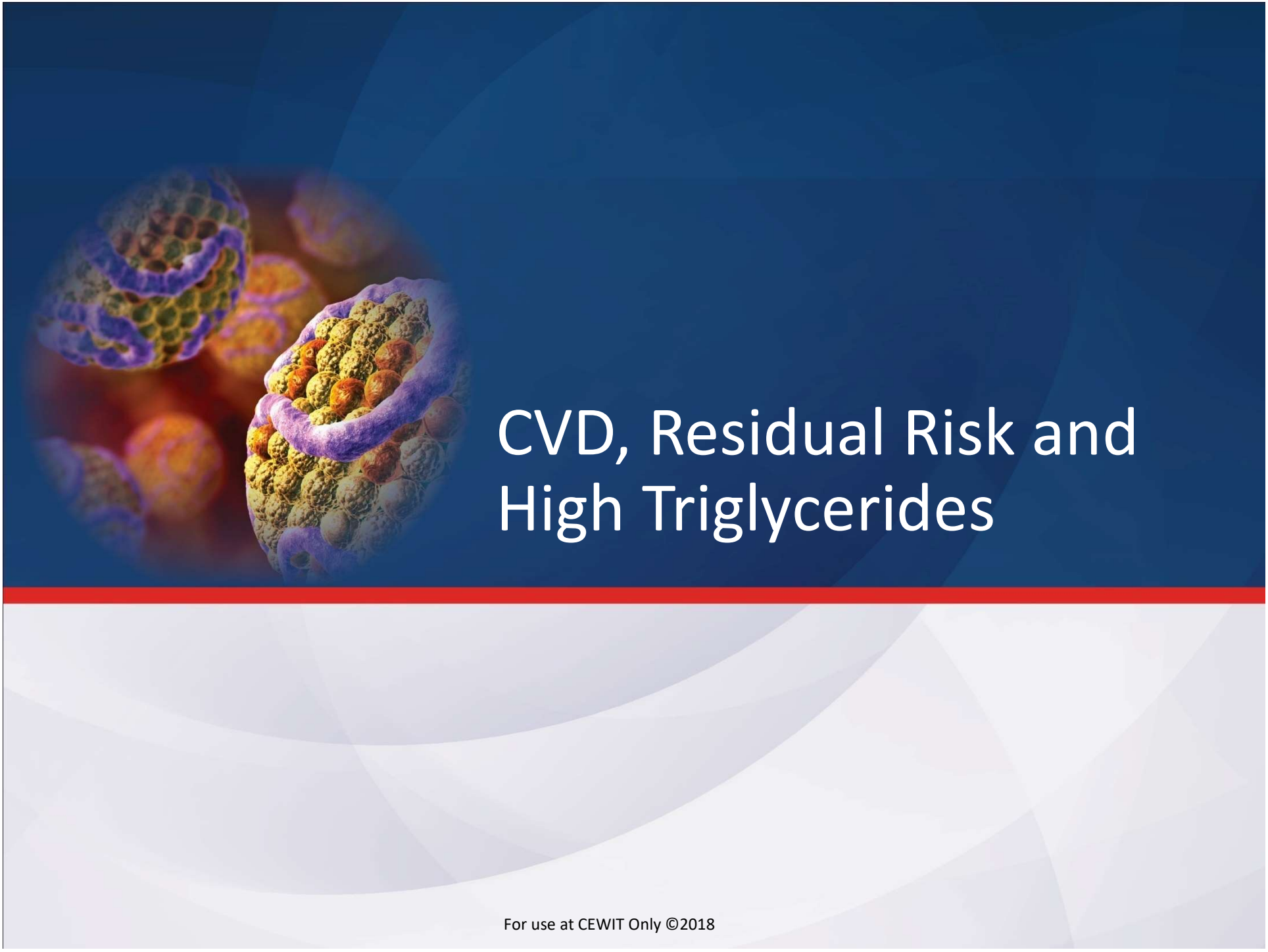
Craig Granowitz, MD, PhD
SVP, Chief Medical Officer
Amarin Pharma, Inc.

Agenda

- Cardiovascular disease remains the leading cause of death
- Residual Risk is a significant health care issue
- Triglycerides are a renewed focus
- Big Data compliments RCTs
- REDUCE-IT CVOT
- Future of Personalized care

“Traditional Definition of Innovation”

- New Mechanism of Action
- Biological Agent (antibody, antisense, siRNA)
- Precise molecular mechanism
- “Breakthrough” efficacy – 25%+ improved efficacy?
- Acceptable Safety
- Little Regard for System – “build it and they will come”

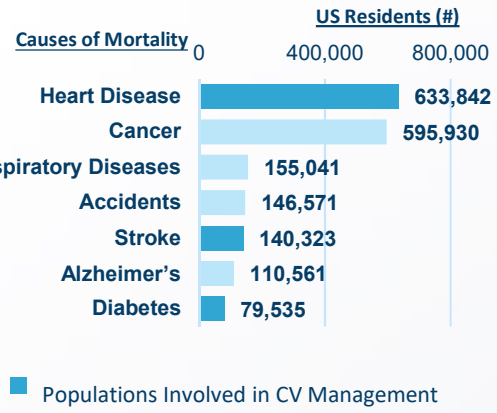


CVD, Residual Risk and High Triglycerides

CV Burden of Disease

CVD is the leading cause of death in the US[1] with an estimated annual cost of nearly $555B nationally[3].

US Number of Deaths by Causes of Mortality (2016)[2]



Morbidity

>800,000 people die
of CV diseases in the US/year[2]

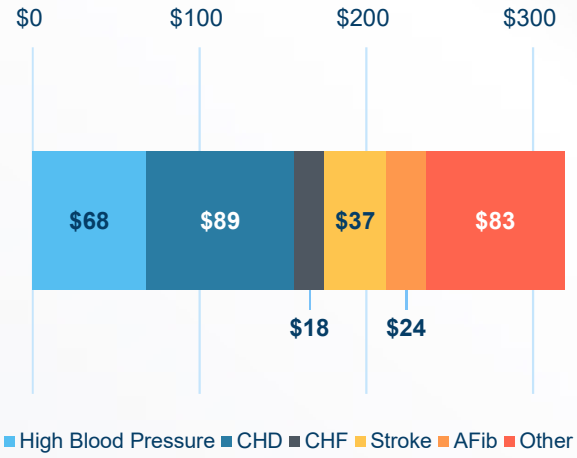
≈1 in Every 3 Deaths[2]

Cost

$555 Billion
estimated total annual cost (direct and indirect)[3]

$1.1 Trillion
within 20 years[3]

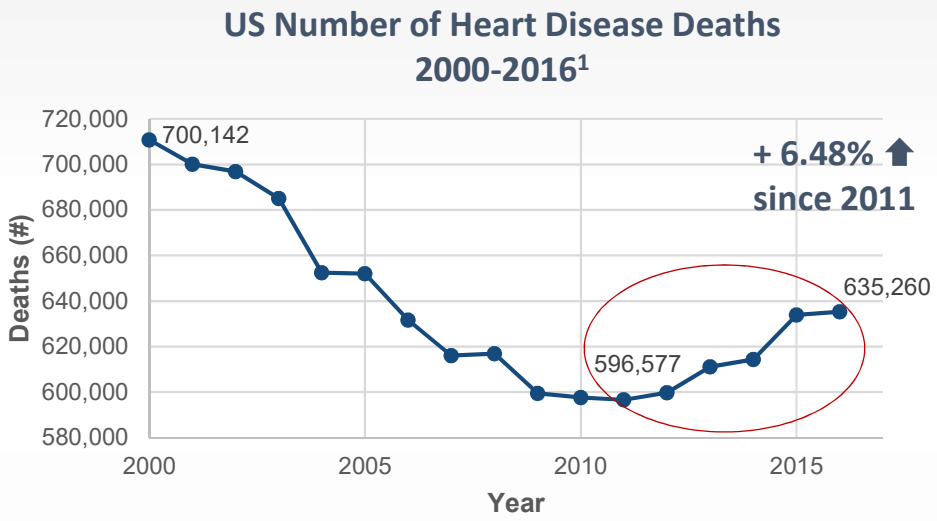
2016 CVD Direct Medical Costs in $Billion[3]



1. Greenlund KJ et al, "Heart disease and stroke mortality in the 20th century". *In*: Ward J, Warren C, eds. *Silent Victories: The History And Practice Of Public Health In Twentieth Century America*. Oxford, England: Oxford University Press; 2006.. 2. Benjamin EJ et al, *Heart Disease and Stroke Statistics – 2018 Update: a Report from the American Heart Association,* [published online ahead of print January 31, 2018]. Circulation. DOI: 10.1161/CIR.0000000000000558. 3. American Heart Association, Cardiovascular Disease: a Costly Burden for America – Projections Through 2035, 2017. Web Apr. 2018

Recent Trends in CV Mortality

According to the Centers for Disease Control (CDC), the number of deaths due to heart disease is on the rise[1]



Overweight and Obesity

- **37.5% adult prevalence** in 2014[2]
- **A 7.7% increase since 2000[2]**

Diabetes

- **23.4 million adults (9.1%) in the US[2]**
- **7.6 million adults (3.1%) with undiagnosed diabetes[2]**

1. Centers for Disease Control, adapted from Heron M, Anderson RN. *NCHS Data Brief*. 2016;(254):1-8. Figure 1: Number of deaths due to heart disease and cancer: United States, 1950-2014 – Completed for years 2015-2016 with Kenneth D. Kochanek MA. *NCHS Data Brief*. 2017; (293): Figure 4: Number of deaths, percentage of total deaths, and age-adjusted death rates for the 10 leading causes of death in 2016: United States, 2015 and 2016. 2. Benjamin EJ et al, Heart Disease and Stroke Statistics – 2018 Update: a Report from the American Heart Association, [published online ahead of print January 31, 2018]. Circulation. DOI: 10.1161/CIR.0000000000000558.

Big Data Compliments RCTs

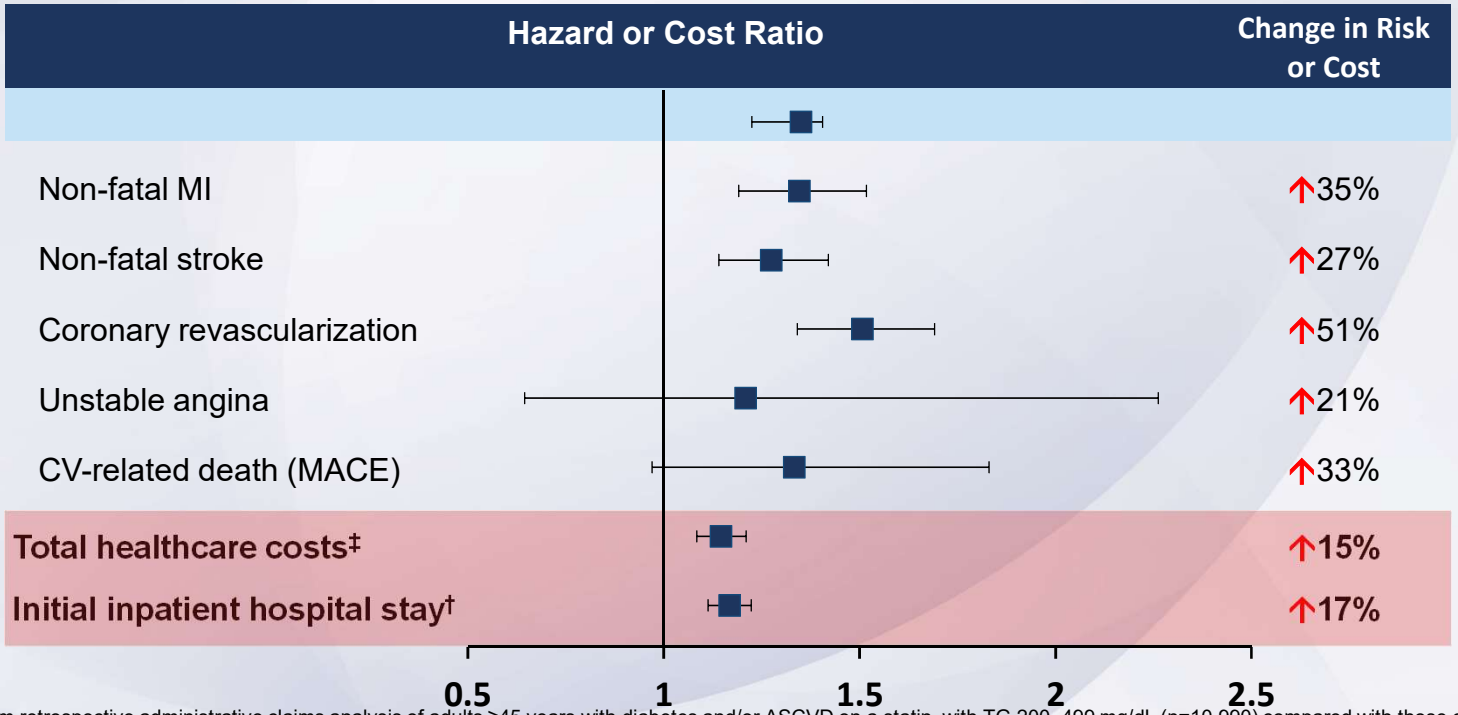
Health-System Collaboration: Using Big Data and Real World Evidence to Improve High-Risk CV Patient Care

We evaluated a cohort of patients similar to those being studied in the REDUCE-IT trial with the following objectives:

- To determine the burden of disease and describe the prevalence of clinical characteristics in this population
- To determine the resource utilization for this cohort
- To determine the incidence of cardiovascular outcomes experienced by this cohort

Real-World Data (OPTUM): HTG Significantly Increased CV Risk and Costs[1,2]

Effect of TG Cohort Variable in Multivariate Analysis of Outcomes*,†



Data from retrospective administrative claims analysis of adults ≥45 years with diabetes and/or ASCVD on a statin, with TG 200–499 mg/dL (n=10,990) compared with those of matched comparator control (TG <150 mg/dL and HDL-C >40 mg/dL, n=10,990). Baseline LDL-C was 106 mg/dL and 101 mg/dL, respectively (*P*<0.001).
HDL-C=high-density lipoprotein cholesterol.*Separate multivariate analyses of major CV events, total health care costs, and initial inpatient stay were performed. Covariates included TG cohort, age, gender, insurance coverage type, geographic region of enrollment, baseline clinical characteristics, and baseline medication use; †Multivariate analysis using Cox proportional hazards model; ‡Generalized linear model. 1. Toth PP et al. Circulation. 2017;136(suppl 1):A15187; 2. Toth PP et al. Presented at the American Heart Association Scientific Sessions 2017, November 11-15, 2017, Anaheim, CA.

What Did Big Data Tell Us?

- Insight into the burden and cost of disease
- Confirmed the REDUCE-IT patient population
- Data to help policy makers, payers and providers make informed decisions
- Model of collaboration between payers, pharma and providers
- Use of new information technology to improve cost, quality and satisfaction

Improving Success Probability Of Pharmaceutical Product Development

- Regulatory requirements are increasing
- What can we learn from biomarker studies? Is there a better option?
- Need for outcome studies
  - 5 years
  - Hundreds of millions of dollars
  - High risk

Cardiovascular Disease Outcomes Trials as an Example

- Statin therapy remains the cornerstone pharmacologic treatment for dyslipidemia and the prevention of CVD
  - Decreases LDL-C and reduces risk
  - Notably, substantial CV risk remains
  - Additional therapy is needed
- CV outcomes studies of the following drug classes, when combined with statin therapy, have shown variable results
  - LDL-C-lowering agents
  - Anti-inflammatory agents
  - A1C-lowering agents
  - TG-lowering agents

Abbreviations on last slide.

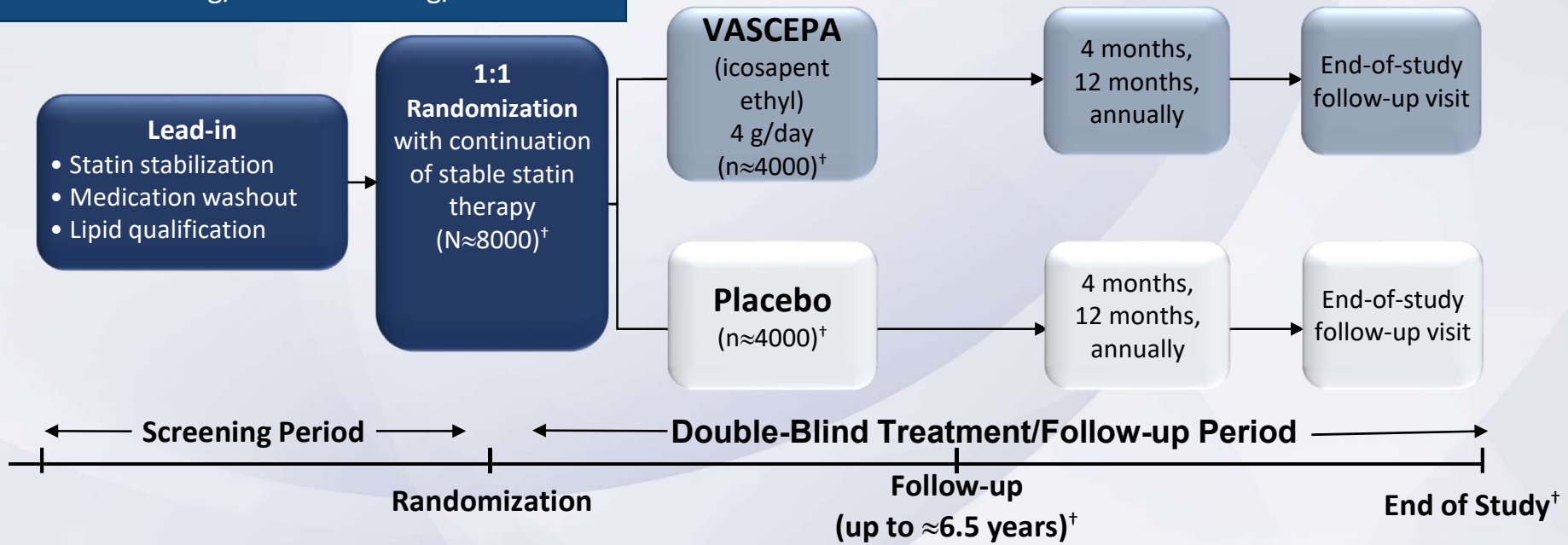
Typical CV Outcome Study

- 5-7 years in Duration
- 10,000+ patients
- 5-20 Countries; 500+ study sites
- $350-$700 million per study
- Required prior to marketing authorization
- Quality Metric Expectations are Rising
- Reimbursement is becoming ever harder
- Post-Approval Commitments

REDUCE-IT: Study Design for CVOT

Key Inclusion Criteria

- Statin treated men & women ≥45 years
- Established CVD (~70T of patients) or T2DM + ≥risk factor
- TG≥150 mg/dL*
- LDL-C >40mg/dL and ≤100 mg/dL



*Study amendment (May 2013) increased the lower end of fasting TG level from ≥150 mg/dL to ≥200 mg/dL to increase enrollment of patients with TGs at or above 200 mg/dL; it is anticipated that mean and median qualifying TG levels will be above 200 mg/dL.

†Final values to be known at study unblinding. Event-driven design: approximately 1612 primary efficacy events will be required during the study; study duration will vary accordingly.

Bhatt DL, et al. Rationale and design of REDUCE-IT: Reduction of Cardiovascular Events with Icosapent Ethyl–Intervention Trial. *Clin Cardiol*. 2017; epub ahead of print.

JB3

Future of Personalized Care

Slide 15

JB3 change to "future of personalized care" to match updated agenda?
Joy Bronson, 9/17/2018

Patients Are at The Limit of Drug Treatment

- "Fab Four"
  - Anti-hypertensives
  - Beta- blocker
  - Statin
  - Anti-platelet agent
- Patients on 8+ medications but risks remain
- Are we at maximum system capacity?
  - How many more can they take?
  - How many more can the healthcare team manage?
  - How many more can the system pay for?

How Do Societies Provide Healthcare that Improves Health with Acceptable Cost and Access?

- Demand for Healthcare increases with
  - Increased Affluence
  - Western Diet and Lifestyle
  - Increased Age
- The World is Growing Older
- Healthcare Productivity is Low

End Result is Exploding Cost or Restricted Access

New Drug Classes that Improve Outcomes

	PCSK-9	GLP-1	SGLT-2	IL-1β Mab	EPA
Proven efficacy	↑	↑	↑	↑	?
Safety	↑	↑↓	↑↓	↑	↑
Ease of Use	↓	↓	↑↓	↓↓	↑
Cost	↑↑↑	↑↑	↑	↑↑↑↑	↓
Fits with treatment paradigm	↓↓	↓↓	↓	↓↓↓	↑

Revised Definition of Innovation; Ideal Attributes of A Drug to Treat Millions

- Proven efficacy
- Excellent safety – proven in registration and in post-marketing wide exposure
- Ease of use (few drug-drug interactions, no complex dosing or delivery)
- Inexpensive system acquisition cost
- No changes needed on current treatment paradigm

Summary

- Cardiovascular disease remains the leading cause of death
- Residual Risk is a significant health care issue
- TGs are a renewed focus
- Big Data compliments RCTs
- REDUCE-IT CVOT
- Future of Personalized care