ALECARDIO

Effect of Aleglitazar on Cardiovascular Outcomes After Acute Coronary Syndrome in Patients With Type 2 Diabetes Mellitus

The AleCardio Randomized Clinical Trial

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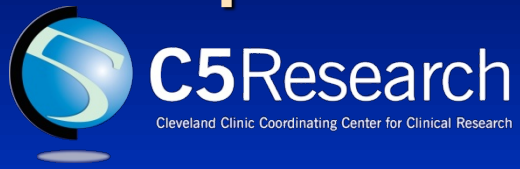
Professor of Medicine

Cleveland Clinic

C5Research
Cleveland Clinic Coordinating Center for Clinical Research

Speaker Disclosure – A. Michael Lincoff, MD

Relationships with Industry Research Sponsors



- Aastrom
- Anthera
- AstraZeneca
- Amgen
- Atricure
- Cardiovascular Systems
- Centocor
- CSL Behring
- Edwards Lifesciences
- Eli Lilly
- Janssen
- Juventas
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- Medtronic
- Omthera
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- Resverlogix
- Roche / Genentech
- Takeda
- The Medicines Co
- Tyrx
- VIVUS

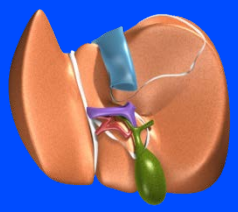
Consultant

- CSL Labs
- Ikaria
- Medscape
- WebMD

Effects of α/γ PPAR Activation

Nuclear receptors that function as transcription factors regulating the expression of genes

α



heart, liver, muscle, vasculature

↑ Fatty acid uptake

↑ Fatty acid oxidation

↑ apo AI, HDL

↓ VLDL-TG

Anti-inflammatory

Primary α effect is to improve plasma lipid profile

↑ Insulin sensitivity

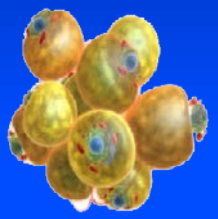
↑ Beta cell function

↑ fatty acid uptake

↑ Adiponectin secretion

Anti-inflammatory

γ



Adipocytes

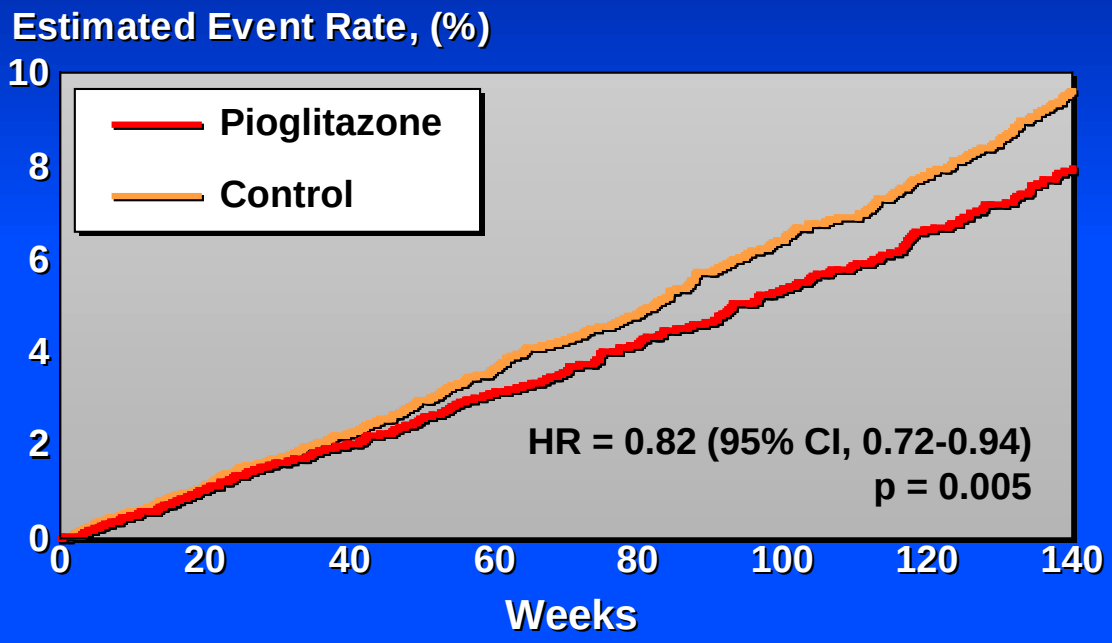
Muscle

Primary γ effect is to improve insulin sensitivity

Pioglitazone - PPAR γ Activator

Meta-Analysis

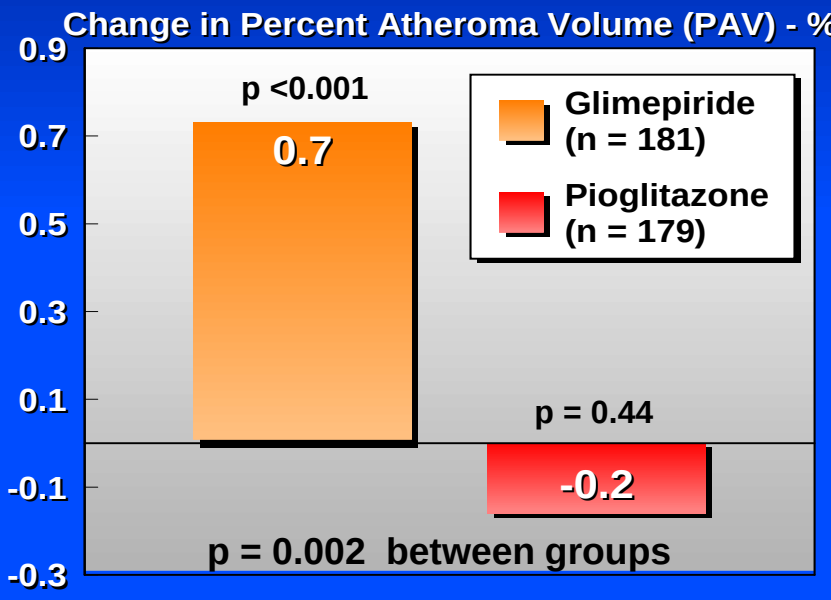
Death, MI, or Stroke – 16,390 Pts



Lincoff et al. JAMA 2007;298:1180-1188.

PERISCOPE Trial

Coronary Intravascular Ultrasound



Nissen et al. JAMA 2008;299:1561.

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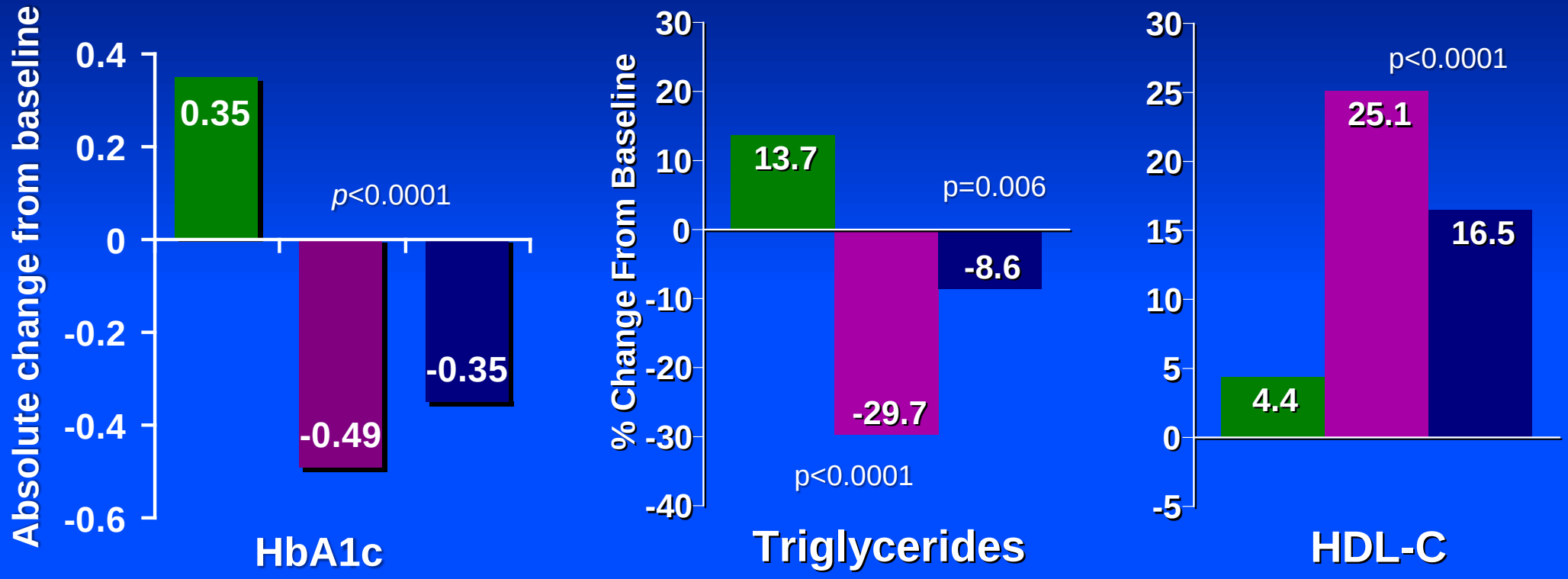
Aleglitazar - Balanced PPAR α/γ Agonist

SYNCHRONY Phase 2 Trial



p-values vs placebo

Placebo n = 55	Aleglitazar 150 mcg n = 55	Pioglitazone 45 mg n = 57

Henry R et al. Lancet 2009;374:126.

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AleCardio trial

Study Hypothesis:

Aleglitazar, added to standard of care of pts with T2DM and recent acute coronary syndrome (ACS), would reduce cardiovascular mortality and morbidity.

- **phase 3**
- **superiority trial**
- **randomized, placebo-controlled, double-blind, multicenter**

Inclusion and Exclusion Criteria

- ✓ Hospitalized with ACS (STEMI, NSTEMI, or UA)
- ✓ Type 2 DM (managed by diet or medication)
- ✓ Patients could be randomized at:
  - hospital discharge for index ACS
  - after screening period of up to 12 wks to allow clinical stabilization, completion of planned revascularization, achievement of steady state renal function.

- x Heart failure – Class II-IV
- x Heart failure hospitalization in prior 12 months
- x Severe peripheral edema
- x CKD - eGFR <45 ml/min-1.73 m^2
- x Fasting triglycerides > 400 mg/dL
- x Ongoing Rx with fibrate or TZD
- x Liver disease
- x Anemia – Hgb <10 mg/dL

Endpoints

Primary

- Time to CV death, non-fatal MI, non-fatal stroke

Secondary

- Time to CV death, non-fatal MI, non-fatal stroke, hosp for UA
- Time to all-cause death, non-fatal MI, non-fatal stroke
- Time to unplanned coronary revascularization

Exploratory

- Glycemic control
- Changes in lipid levels

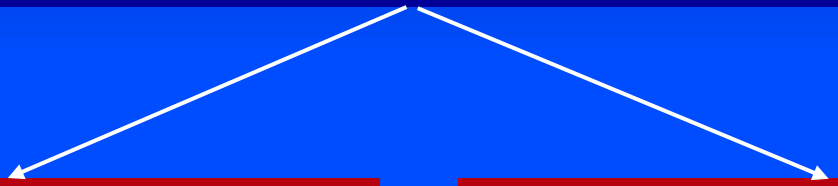
Safety

- Hospitalization due to heart failure
- Renal safety composite – (ESRD, doubling SCr, 50% increase in SCr leading to study drug D/C)
- AEs of special interest – fluid retention, edema, weight, bone fx, hypoglycemia, malignancies

ALECARDIO Trial Design

Type 2 DM and recent Acute Coronary Syndrome
(STEMI, NSTEMI or UA)

N ~ 7000 Patients Randomized
Double blind, 1:1 Ratio
Up to 12 weeks after index event



Aleglitazar
150 μg/day in morning

Placebo

Study visits: 1, 3, 6, 9, 12 mos, then alternative visits and phone q3 mos

Event Driven – 950 positively-adjudicated 1º Endpoint events
Anticipated ~2.5 years follow-up

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Trial Design

Statistics

- Primary efficacy analysis using intention-to-treat (ITT) population
- Placebo group event rate 10% 1st year, 4% annually thereafter
- 20% relative risk reduction with aleglitazar
- $\alpha = 0.01$ (2-sided); $\beta = 0.80$ by log-rank test

→ Accrual of 950 positively-adjudicated primary endpoint events

→ Initial sample size – 6000 pts over 2.5 yr follow-up

→ Observed event rate lower than expected – size increased to 7000 pts

- Interim analysis was planned at accrual of 80% of expected 1º endpoint events (760 of required 950) for early termination for:
  - efficacy – P<0.001
  - futility – conditional power <10% for two-sided P<0.05

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Trial Leadership

Executive Steering Committee		DSMB
A. Michael Lincoff - Chair	Stephen Nicholls	Paul Armstrong - Chair
Diederick Grobbee – Co-PI	Lars Ryden	David L. DeMets
Jean-Claude Tardiff – Co-PI	Gregory C. Schwartz	Philip Home
John Buse	Hans Wedel	John McMurray
Robert Henry	Klas Malmberg - Roche	Lynda Szczech
Bruce Neal	Arlette Weichart - Roche	Patrick S. Parfrey

Consortium of 5 Academic Research Organizations (AROs)

- Cleveland Clinic Coordinating Center for Clinical Research (C5Research)
- Montreal Heart Institute Coordinating Center (MHICC)
- Julius Clinical Research, University Health Center Utrecht (JCR)
- George Institute for Global Health
- Berman Center for Outcomes and Clinical Research

Roche

C5Research
Cleveland Clinic Coordinating Center for Clinical Research

Montreal Heart Institute Coordinating Center | MHICC

AACT
ACADEMIC ALLIANCE FOR CLINICAL TRIALS

ALECARDIO Enrollment and Nat'l Coordinators

7226 Pts. 26 Countries, 720 Sites: Feb 2010 – May 2012

USA	Bittner, Grimm, McGuire, Steinhubl, Wright	1,104
Poland	Ponikowski	638
China	Dayi	630
India	Sethi	600
Canada	Ibrahim	545
Brazil	Nicolau	533
Spain	Bruguera	449
Mexico	Leiva	369
Germany	Munzel	279
Hungary	Keltai	251
Korea	Kim	232
Thailand	Tresukosol	231
Italy	Savonitto	157

Argentina	Conde	156
United Kingdom	Poulter	134
Sweden	Melbin	132
Czech Republic	Solar	124
Malaysia	Sim	119
Australia	Brieger	98
Netherlands	Jukema	94
France	Montalescot	92
Romania	Veresiu	90
New Zealand	Troughton	60
Ireland	McAdams	43
Russia	Baranova	41
Denmark	Clemmensen	28

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Baseline Characteristics

	Aleglitazar N = 3616	Placebo N = 3610
Age (yr) – mean +/- SD	61 +/- 10	61 +/- 10
Weight (kg) – mean +/- SD	82.9 +/- 18.9	83.3 +/- 19.1
BMI – median (IQR)	28.6 (25.6-32.1)	28.7 (25.7-32.5)
Newly-diagnosed T2 DM (%)	10.1	10.7
Duration of T2 DM (yr) – mean +/- SD	8.6 +/- 7.5	8.6 +/- 7.8
History of CHF (%)	10	10
ACS Index Event		
STEMI (%)	39	40
NSTEMI (%)	36	37
Unstable angina (%)	25	24
Diabetes medications (%)		
Metformin / Sulfonylureas / Insulin	67 / 35 / 29	66 / 34 / 30
Cardiac medications (%)		
Aspirin / ADP Inhibitor	96 / 89	95 / 87
Statin	92	93

ALECARDIO Data Safety Monitoring Board

Early Termination of Trial

- identified higher incidence of specific adverse events in aleglitazar group
- directed *unplanned* futility analysis to be performed for 8th scheduled meeting

Unplanned interim analysis – 522 adjudicated events (55% of projected total)

HR = 1.01 [95% CI 0.85-0.19, P = 0.95]

Futility analysis - <1% conditional power for superiority to P<0.05

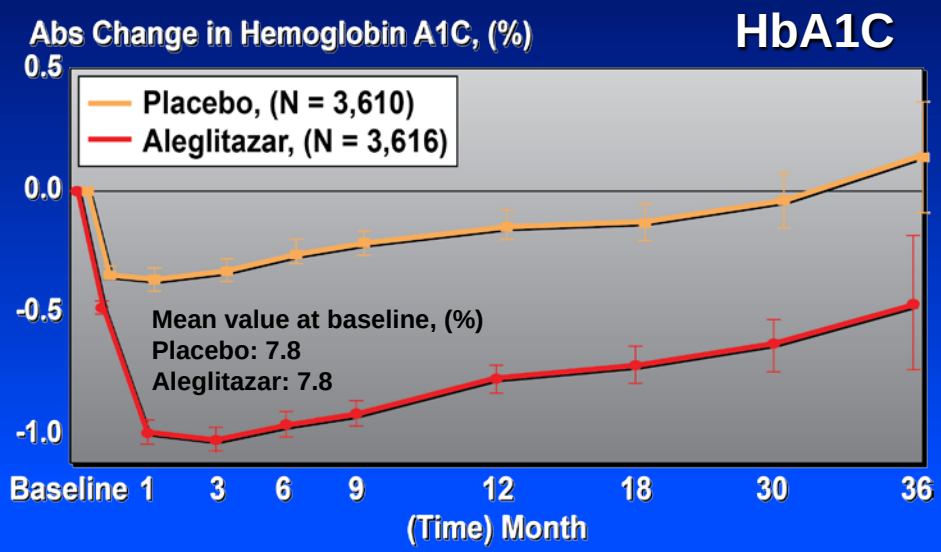
- DSMB recommended termination of trial for futility
- Exec Committee and Sponsor agreed – trial terminated July 2, 2013

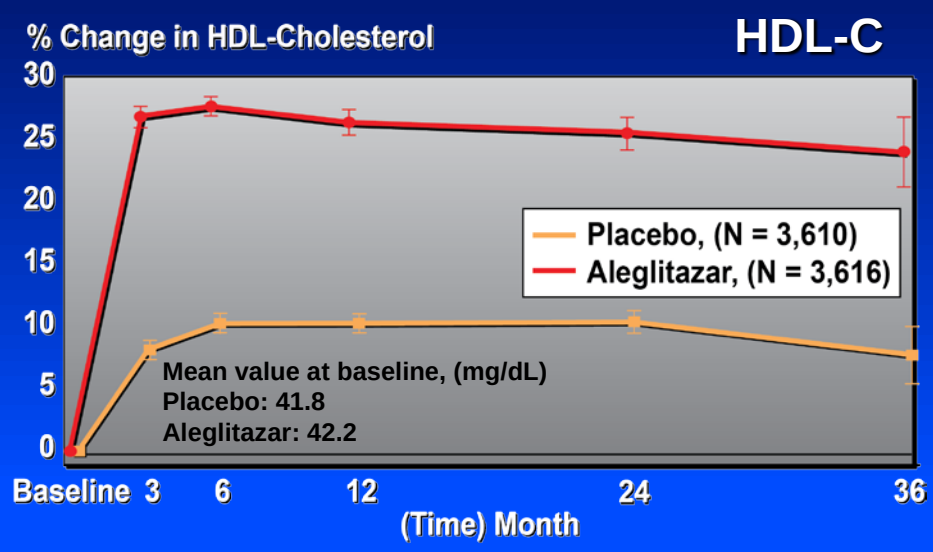
Finalization of trial database on December 17, 2013:

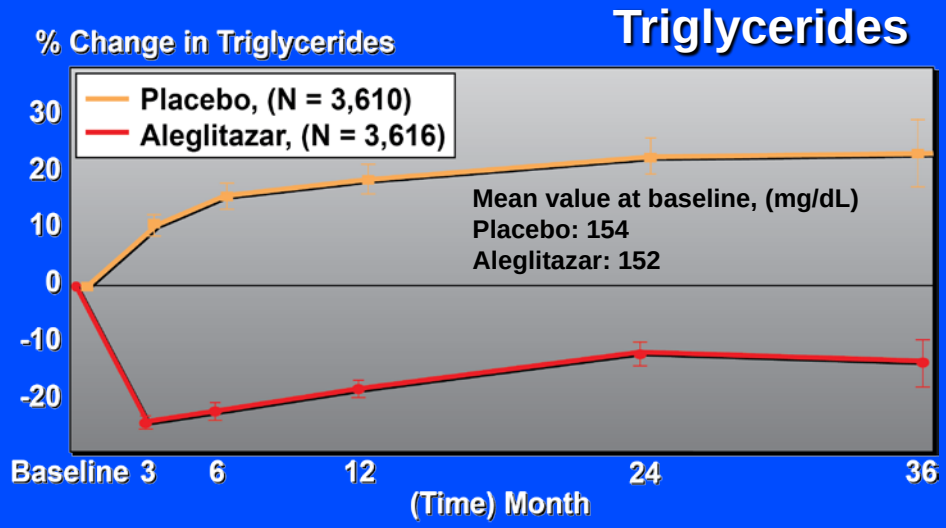
704 adjudicated primary endpoint events – 74% of predicted

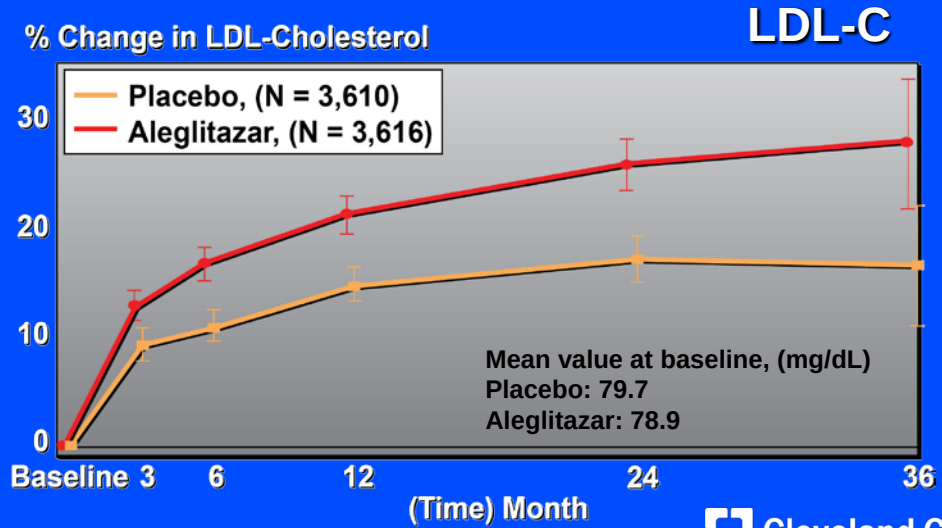
Median follow-up – 104 weeks (IQR 82-129)

ALECARDIO Glycemic Control and Lipids









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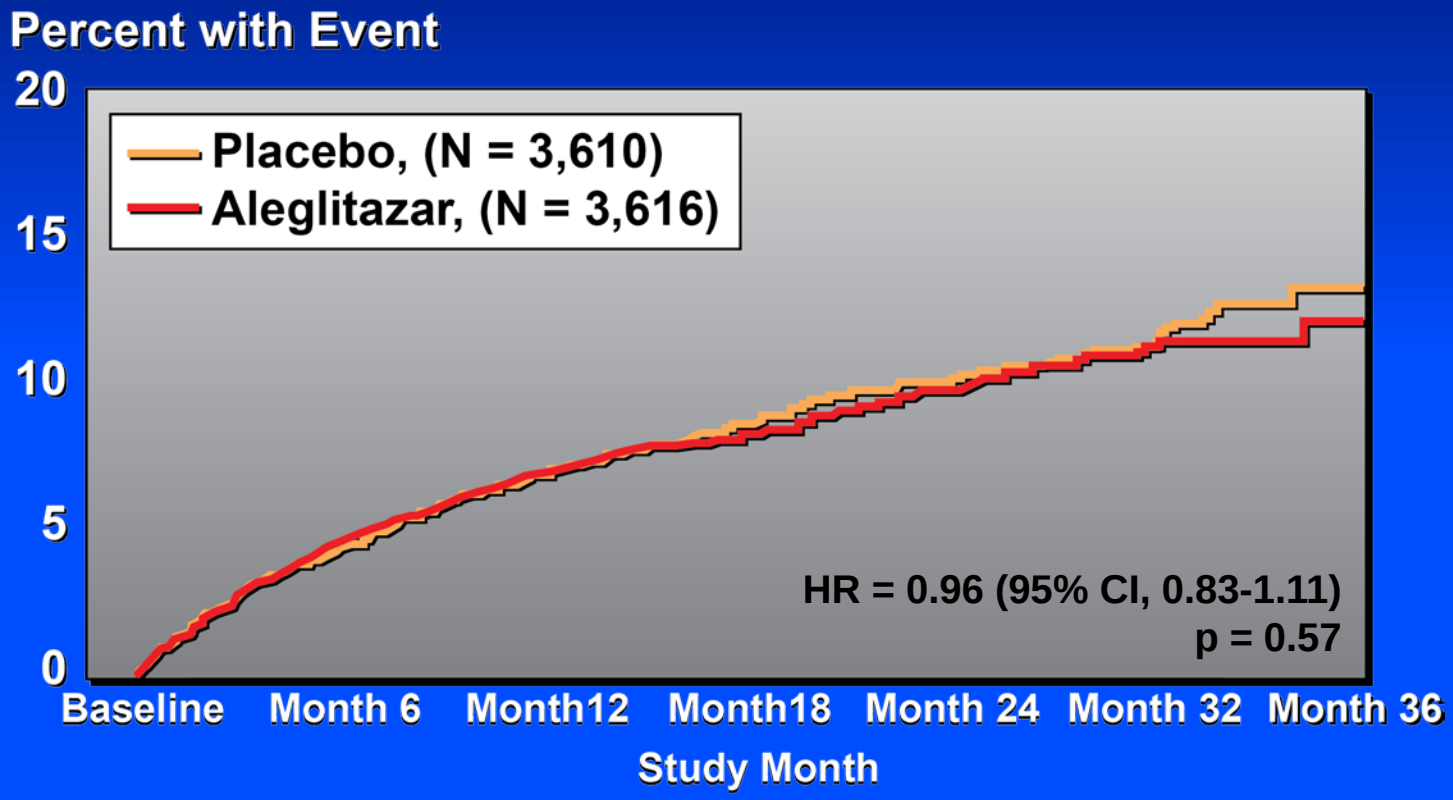
ALECARDIO Primary Efficacy Endpoint

Cardiovascular Death, Non-Fatal MI, Non-Fatal Stroke



No. at risk:							
Placebo	3610	3394	3252	2720	1706	773	118
Aleglitazar	3616	3387	3249	2731	1688	780	101

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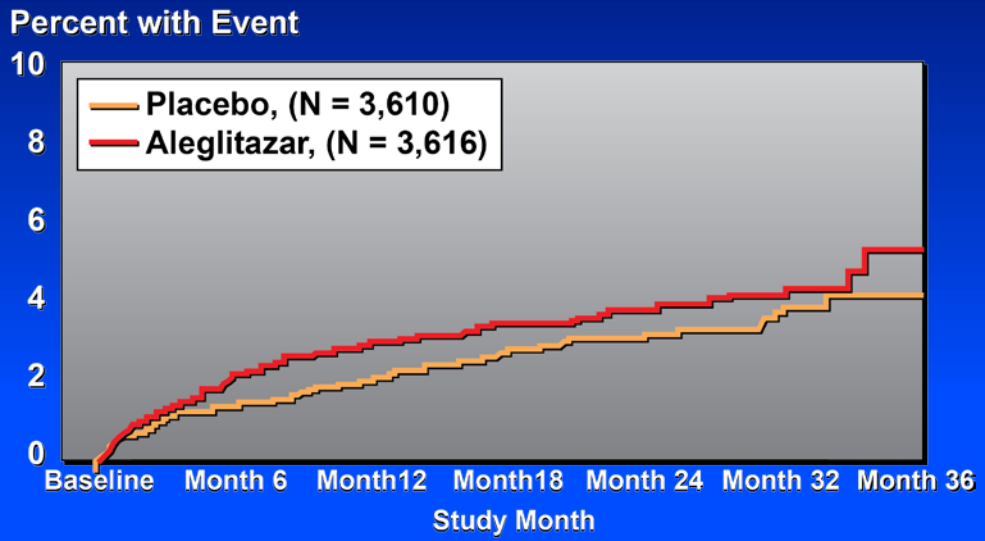
Efficacy Outcome

Cardiovascular Efficacy Endpoints

Number of Patients (%)	ALE N = 3616	PLAC N = 3610	HR (95% CI)	P
1º Composite – CVD, MI, stroke	344 (9.5)	360 (10.0)	0.96 (0.83-1.11)	0.57
CV death, MI, stroke, UA hosp	441 (12.2)	488 (13.5)	0.90 (0.79-1.02)	0.11
Death, MI, stroke	373 (10.3)	392 (10.9)	0.95 (0.83-1.10)	0.51
Death from any cause	148 (4.1)	138 (3.8)	1.08 (0.85-1.36)	0.54
CV Death	112 (3.1)	98 (2.7)	1.15 (0.87-1.50)	0.32
Non-fatal MI	212 (5.9)	239 (6.6)	0.89 (0.74-1.07)	0.22
Non-fatal stroke	49 (1.4)	50 (1.4)	0.98 (0.66-1.45)	0.92
Unstable angina hospitalization	118 (3.3)	155 (4.3)	0.75 (0.59-0.96)	0.02
Unplanned Revascularization	397 (11.0)	498 (13.8)	0.79 (0.69-0.90)	<0.001

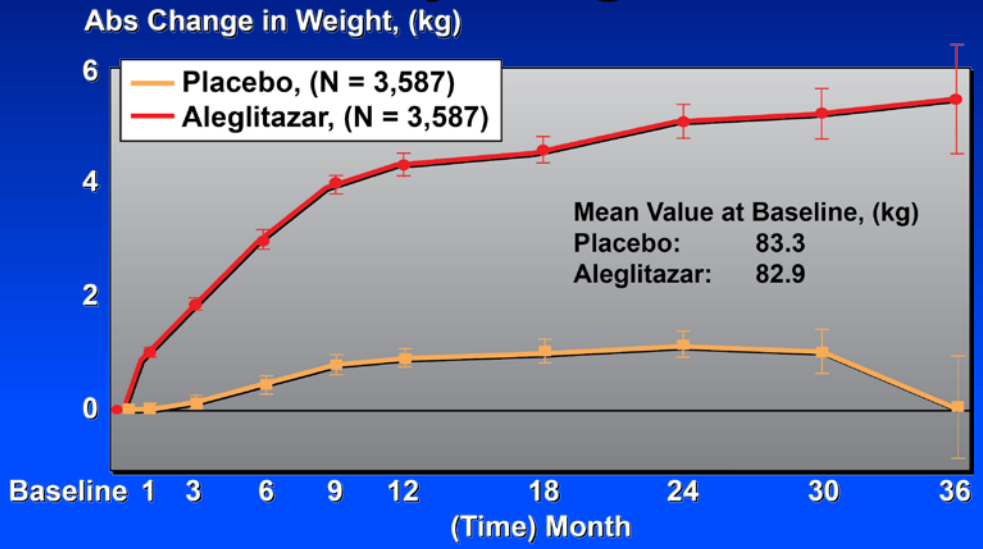
ALECARDIO Heart Failure/Fluid Retention

Hospitalization for HF



HR = 1.22 (95% CI, 0.94-1.59)
p = 0.14

Body Weight



4.6 kg vs. 0.9 kg, P <0.001

Heart Failure Serious Adverse Event:
Aleglitazar 4.7% vs Placebo 3.8%, HR 1.24; 95% CI 0.99 to 1.66, P = 0.06

Peripheral Edema:
Aleglitazar 14.0% vs Placebo 6.6%, P <0.001

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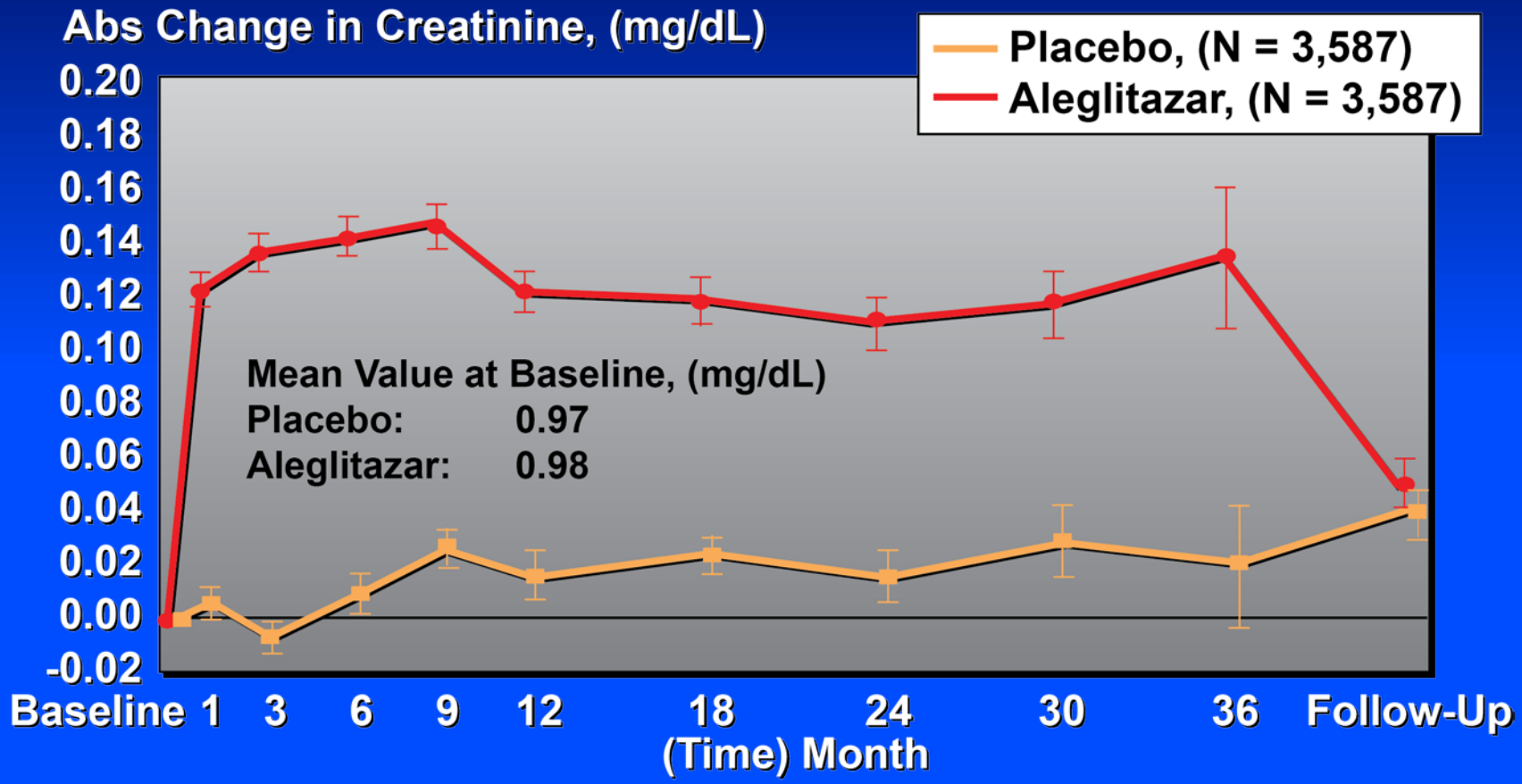
Renal Function

Change in Creatinine



Composite Renal Endpoint:

Aleglitazar 7.4% vs Placebo 2.7%, HR 2.85; 95% CI 2.25 to 3.60; P <0.001

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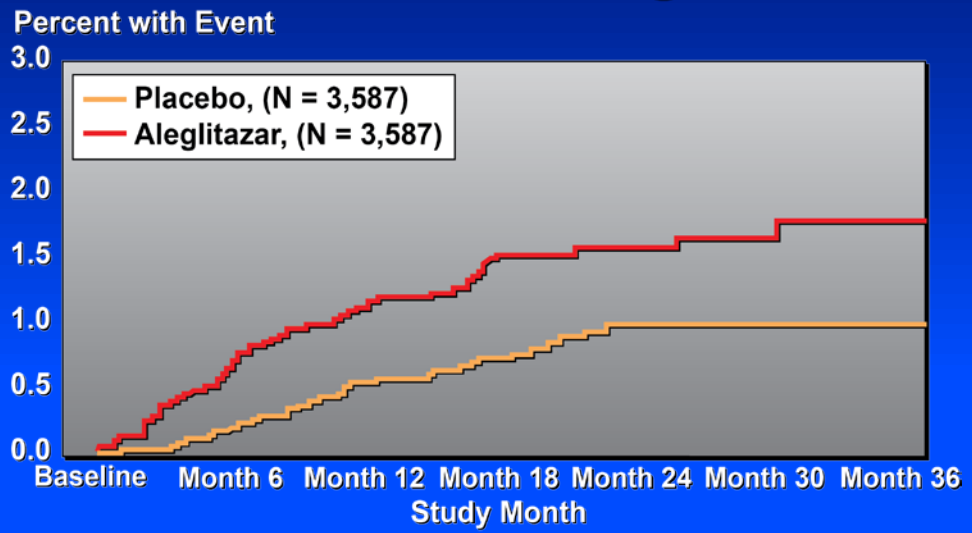
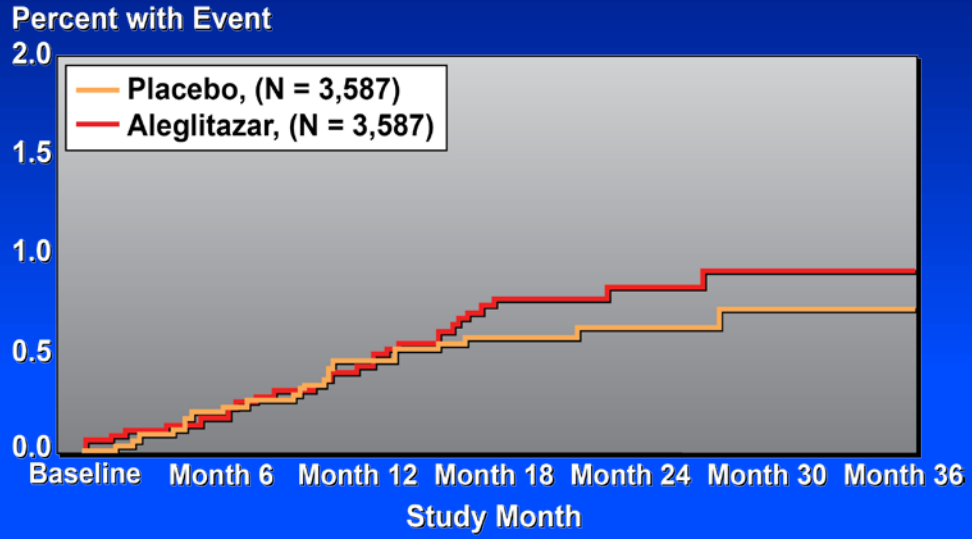
Safety Endpoints

GI Hemorrhage



Hazard Ratio 1.44; (95% CI, 1.03 - 2.00)
Log-rank P = 0.03

Bone Fractures



Hazard Ratio 1.30; (95% CI 0.94 - 1.80)
Log-rank P = 0.11

Hypoglycemia (at least one event):

Aleglitazar 17% vs Placebo 11%
HR 1.60; 95% CI 1.41 to 1.82; P <0.001

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Summary

Conclusions

When added to standard of care of patients with Type 2 diabetes and recent ACS, the dual PPAR-activator aleglitazar:

- reduced glycated hemoglobin
- improved levels of triglycerides and HDL-C
- did not reduce the risk of cardiac mortality, MI, or stroke
- increased risk of heart failure, renal dysfunction (reversible), bone fractures, GI hemorrhage, and hypoglycemia.

Adverse effects highlight difficulties involved in development of PPAR activating drugs - unique patterns of gene modulation result in complex effects on metabolic pathways and unpredictable therapeutic profiles.

These findings do not support the use of aleglitazar to reduce CV risk.

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