
Update Diabetes Therapie
Universitätsspital Basel
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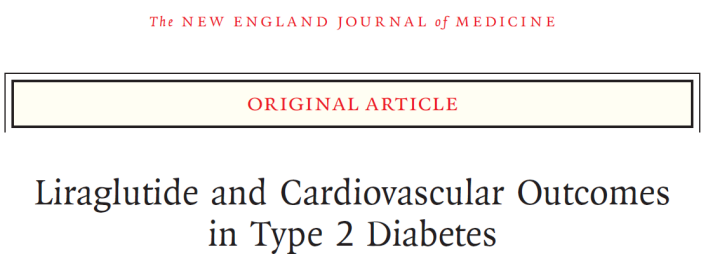
Endokrinologie, Diabetologie
und Metabolismus
Geburt und
Gynäkologische Notfälle
Universitätsspital Basel

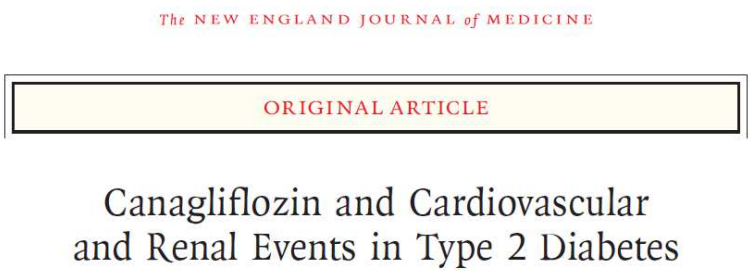
Recent CV outcome studies in Diabetes

- N Engl J Med. 2015 373:2117-28
  (Empa-Reg outcome study)

- N Engl J Med. 2016 June 13
  (LEADER trial)

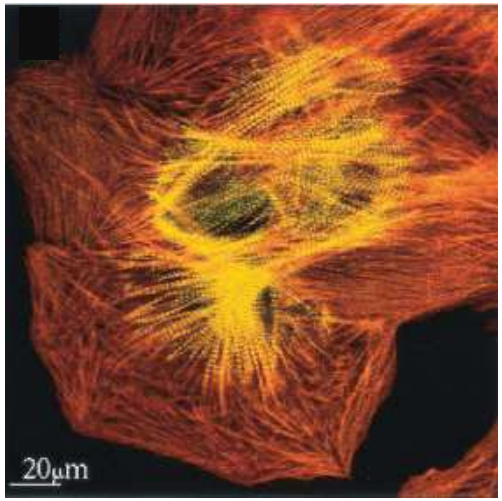


- N Engl J Med. 2017 June 12
  (CANVAS trial)

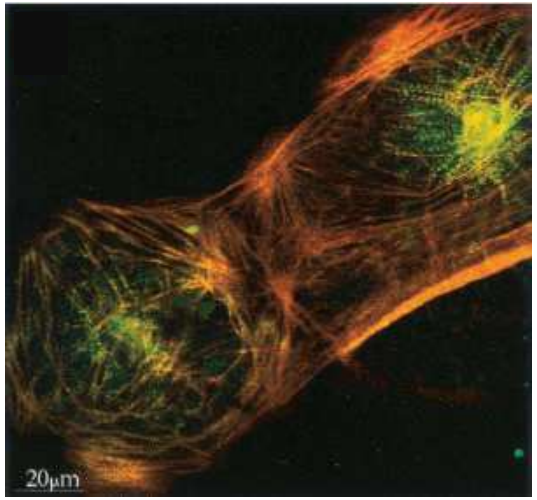


Cardiomyocytes

Control



Glucose

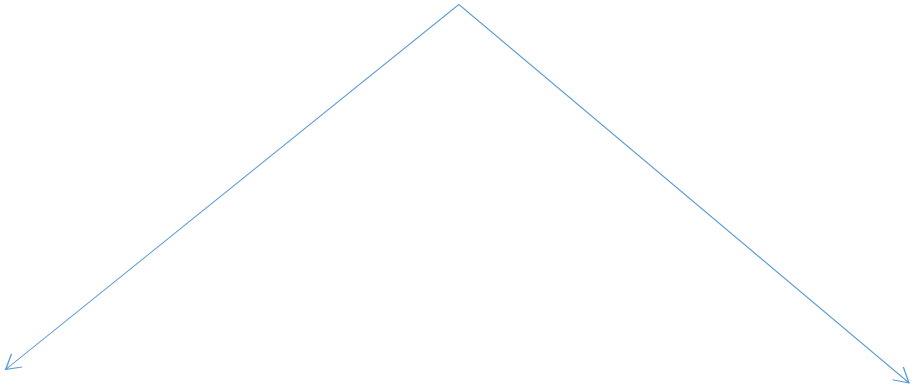


Dyntar et al. Diabetes 50: 2105-13

Type 2 diabetes

=

Protection against Overnutrition



Islet:

Protection

=

Insulin production↓

Fat, liver, muscle:

Protection

=

Insulin sensitivity ↓

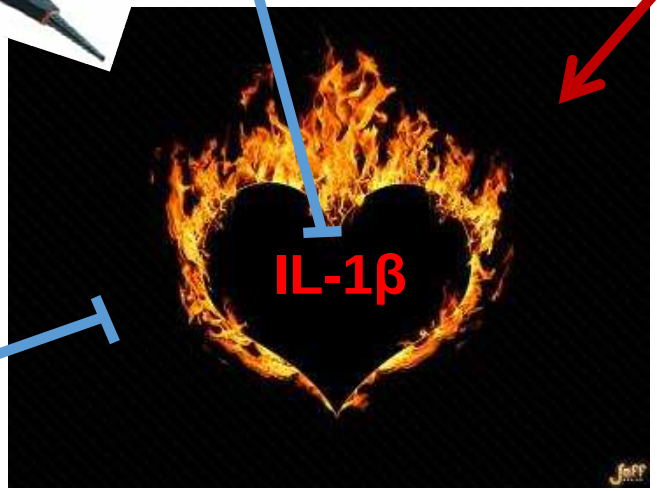
Treatment of Typ 2 Diabetes

GLP-1

Insulin
sulfonylureas

Anti-IL-1β

Metformin



Sport
SGLT2i
Bariatric surgery

UCP-1

Therapie targets

- Microvascular: HbA1c

- Macrovasular: Multifactorial:
  - Nutrient
    → Life Style, GLP1a, SGLT2i, Bariatric surgery
  - Lipid
    → Statin, PCSK9i
  - Blood pressure

- Heart failure

Glycemic targets

- HbA1c < 7.0%

Individualization is key:

- Tighter targets (6.0 - 6.5%)

- younger, healthier

- Looser targets (7.5 - 8.0%)

- older, comorbidities, hypoglycemia prone, etc.

- Avoidance of hypoglycemia

Treatment of Typ 2 Diabetes

1. Prevention – Life-style intervention
   - ➢ Sport is the best drug
2. Anti-obesity treatment
   - ➢ GLP-1, GLP1-Glucagon etc.
3. Glucose lowering without tissue accumulation
   - ➢ SGLTi, bariatric surgery
4. Damage limitation
   - ➢ DPP-IVi, Anti-inflammation

Lifestyle:
Future or past?

Exercise improves

- **Well beeing**
- **Glucose uptake in muscles**
- **Insulin production (cross-talk muscle-islet)**
- **Body weight (?)**

Incretins

- DPP-IV inhibitors
- GLP-1 analoga

DPP-IV inhibitors

- No Hypoglycaemia
- No changes in Body weight
- Safe

But no demonstrated cardiovascular protection

DPP-IV inhibitors

- Sitagliptin (Januvia und Xelevia bzw. Janumet & Velmetia)
- Vildagliptin (Galvus und Galvumet)
- Saxagliptin (Onglyza und Kombiglyze XR)
- Linagliptin (Trajenta und Jentadueto)

GLP-1 analoga

Twice-daily

- Exenatide (Byetta)

Daily

- Liraglutide (Victoza) & Liraglutide & Degludec (Xultophy)
- Lixisenatid (Lyxumia) & Lixisenatid & Glargin (Suliqua)

Once-weekly

- Exenatide Once Weekly Sustained-release (Bydureon)
- Dulaglutide (Trulicity)
- Semaglutide (Ozempic)

SGLT2 Inhibitors

1. Canagliflozin (Invokana)
2. Dapagliflozin (Forxiga)
3. Empagliflozin (Jardiance)

SGLT2 Inhibitors

- HbA1c↓
- Body weight ↓(80-100 gr. glucose = ~ 300-400 cal/day)
- Blood pressure ↓
- No hypoglyceamia
- All combination possible (incretin limits)

BUT:

- Genital infections
- Ketoacidosis
- New drug (Glucagon secretion ↑, Osteoporosis ?)

Therapeutic schema

1. Lifestyle
2. Metformin
3. Individualization :
   A. Early case: Gliptin or GLP-1analog (BMI>28)
   B. Established cardiovascular disease: SGLT2i or GLP-1analog
   C. Uncontrolled diabetes or GFR < 30 : Basal insulin (& GLP-1analog)
   D. BMI>35: consider bariatric surgery

The NEW ENGLAND JOURNAL of MEDICINE

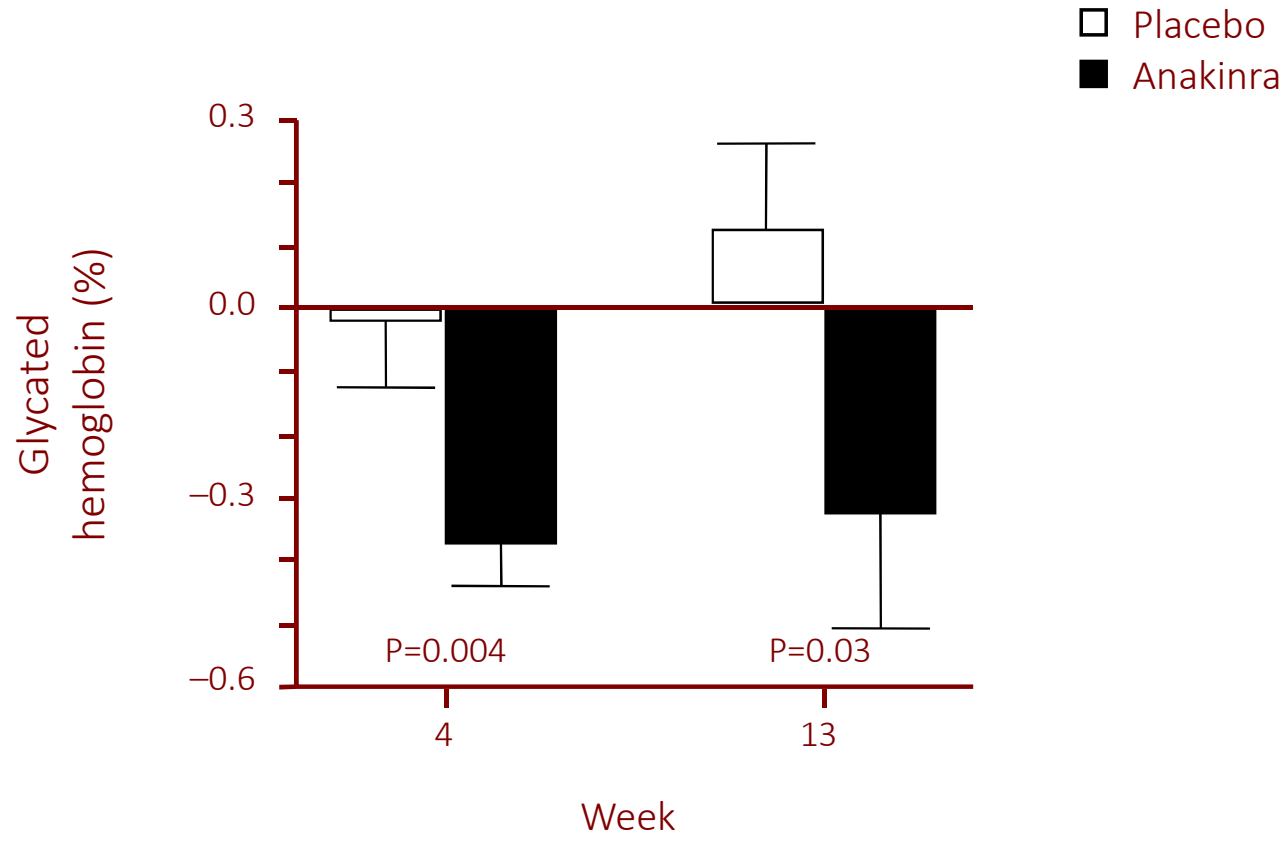
ORIGINAL ARTICLE

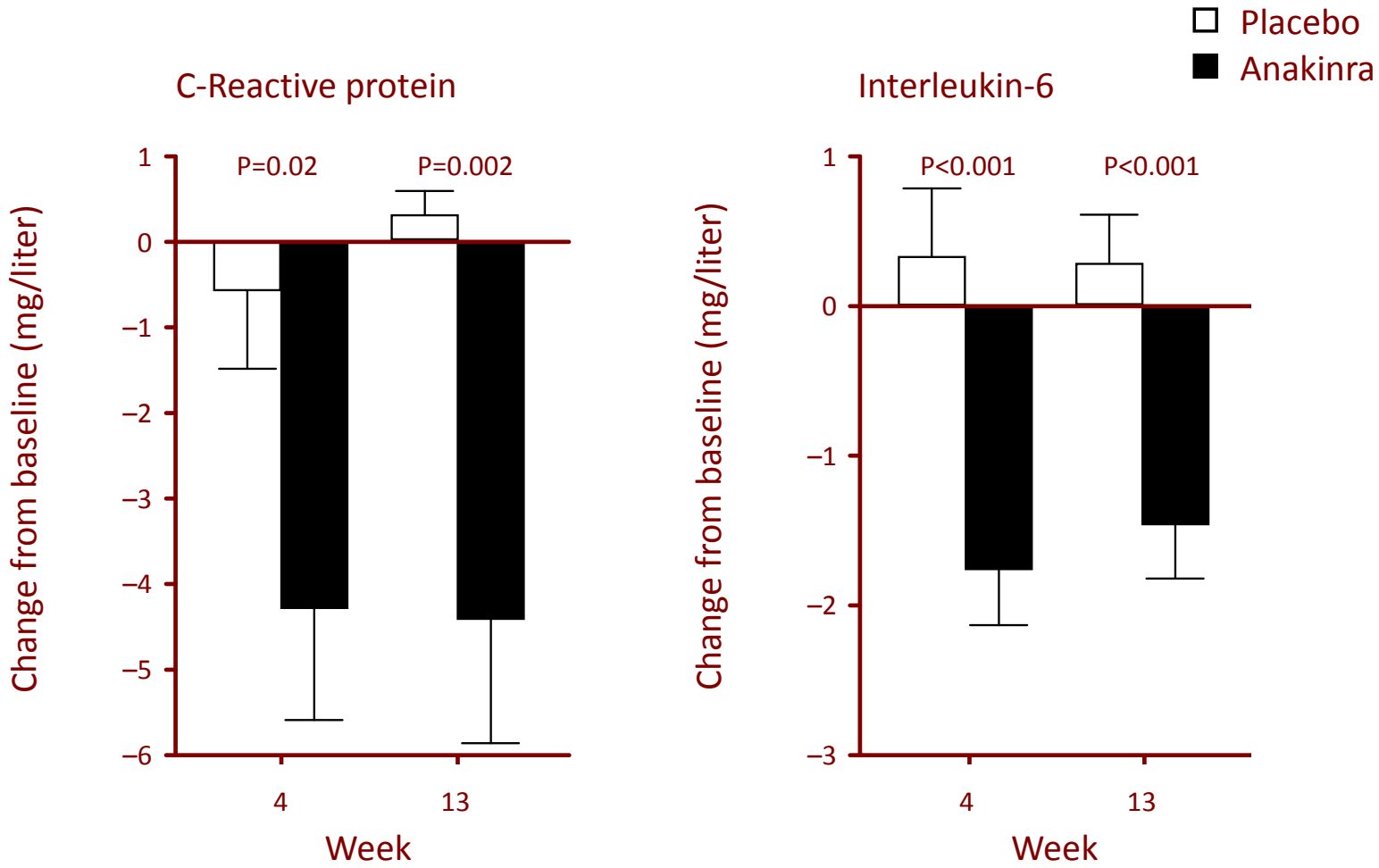
Interleukin-1–Receptor Antagonist in Type 2 Diabetes Mellitus

Claus M. Larsen, M.D., Mirjam Faulenbach, M.D., Allan Vaag, M.D., Ph.D., Aage Vølund, M.Sc., Jan A. Ehses, Ph.D., Burkhardt Seifert, Ph.D., Thomas Mandrup-Poulsen, M.D., Ph.D., and Marc Y. Donath, M.D.

NEJM 356: 1517

Primary endpoint: change in HbA_{1c} at 13 weeks



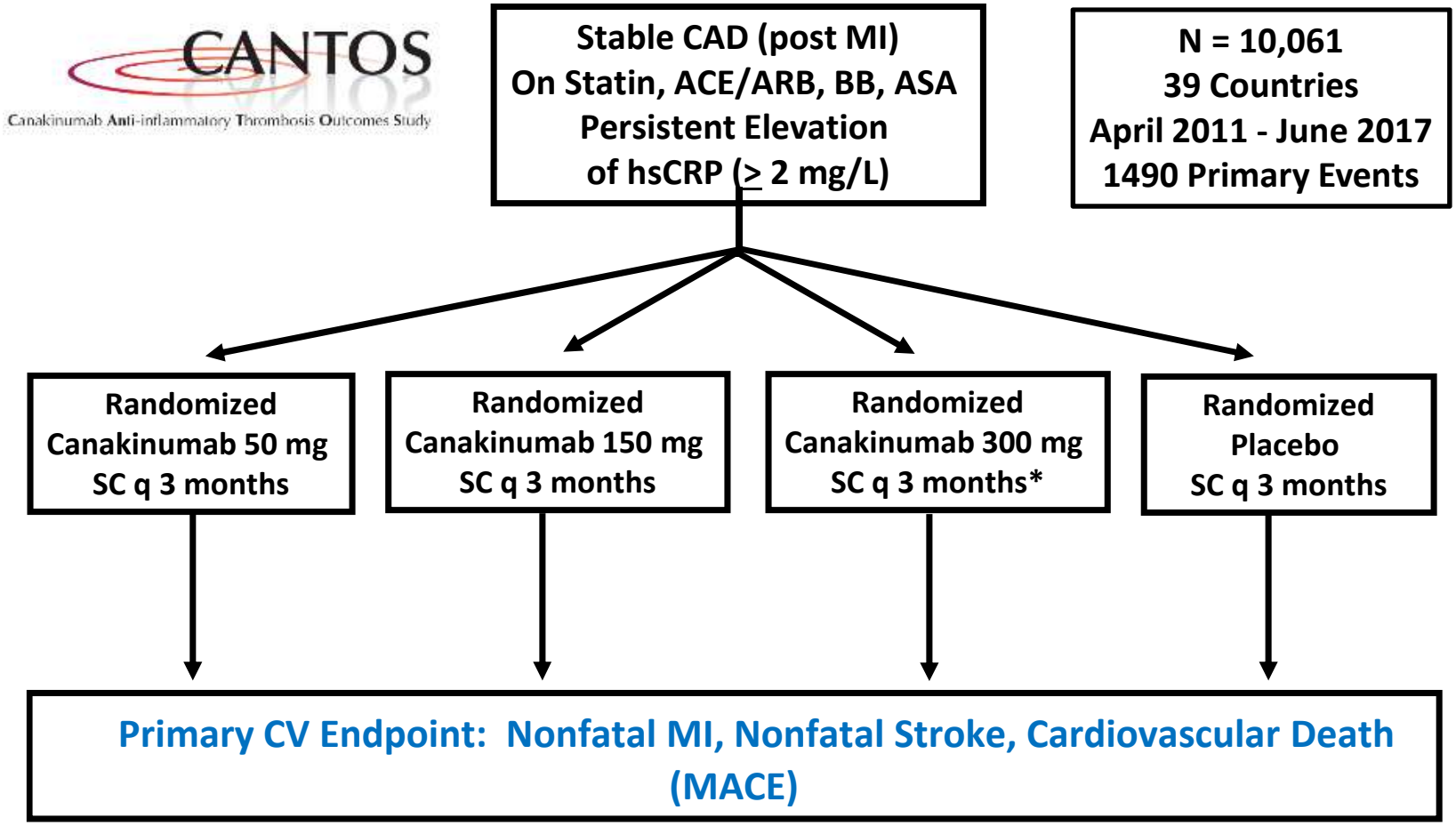

Placebo
Anakinra
C-Reactive protein
Interleukin-6
Change from baseline (mg/liter)
P=0.02
P=0.002
P<0.001
P<0.001
1
0
−1
−2
−3
−4
−5
−6
4
13
Week

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)



Ridker ESC 2017

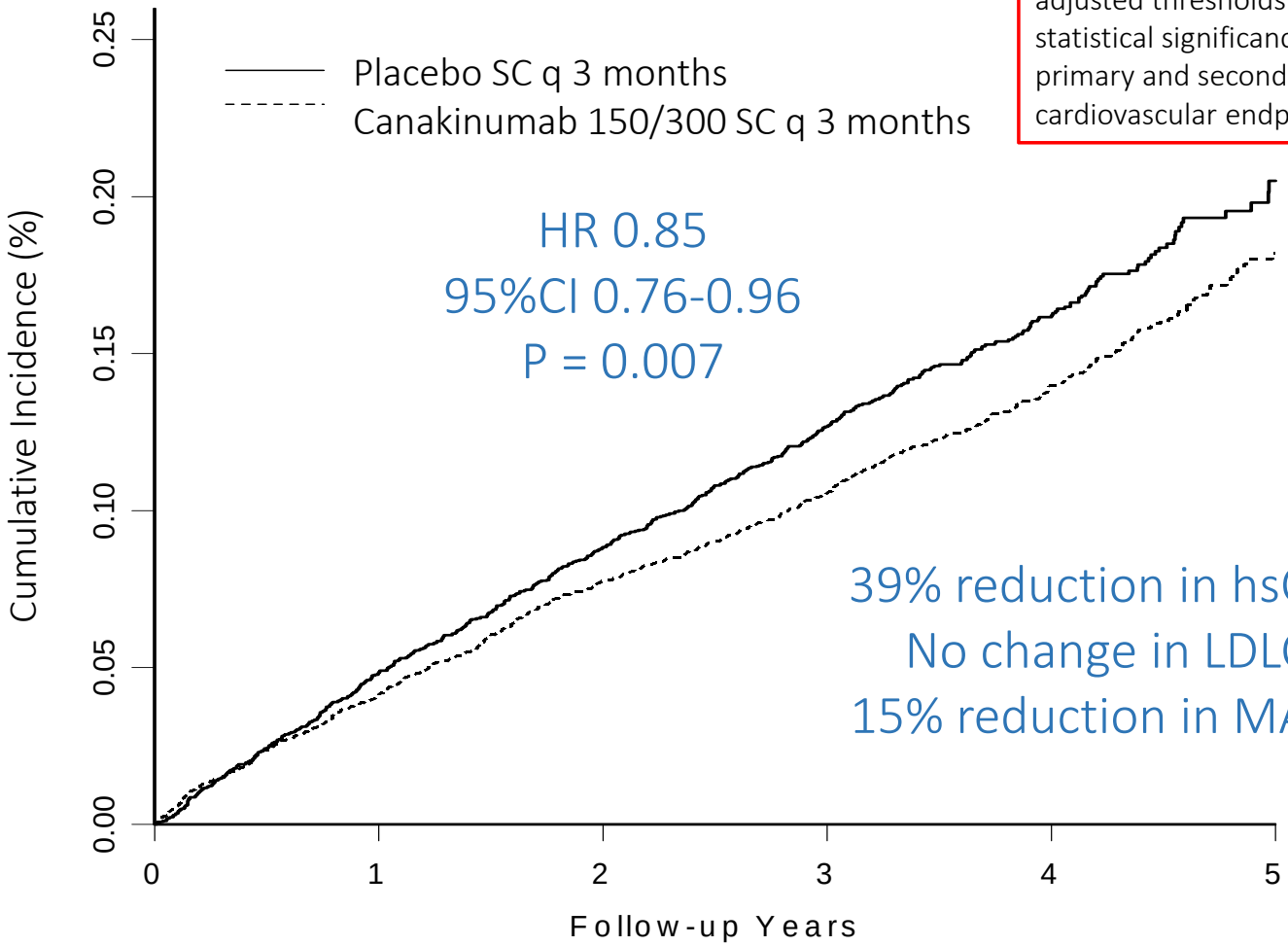
CANTOS - Baseline Clinical Characteristics

		Canakinumab SC q 3 months		
Characteristic	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)
Age (years)	61.1	61.1	61.2	61.1
Median body-mass index (IQR)	29.7	29.9	29.8	29.8
Diabetes (%)	39.9	39.4	41.8	39.2
Prediabetes (%)	49	49	49	49
Hypertension (%)	79.1	80.7	79.4	79.5
Renin-angiotensin inhibitors (%)	79.8	79.3	79.8	79.6
Statin (%)	91.1	91.7	90.6	91.1
hsCRP (mg/L)	4.1	4.1	4.2	4.1

⇒ Population with metabolic syndrome

CANTOS: Primary Cardiovascular Endpoint (MACE)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints



Ridker PM et al, NEJM 2017 [DOI:10.1056/NEJMoa1707914]

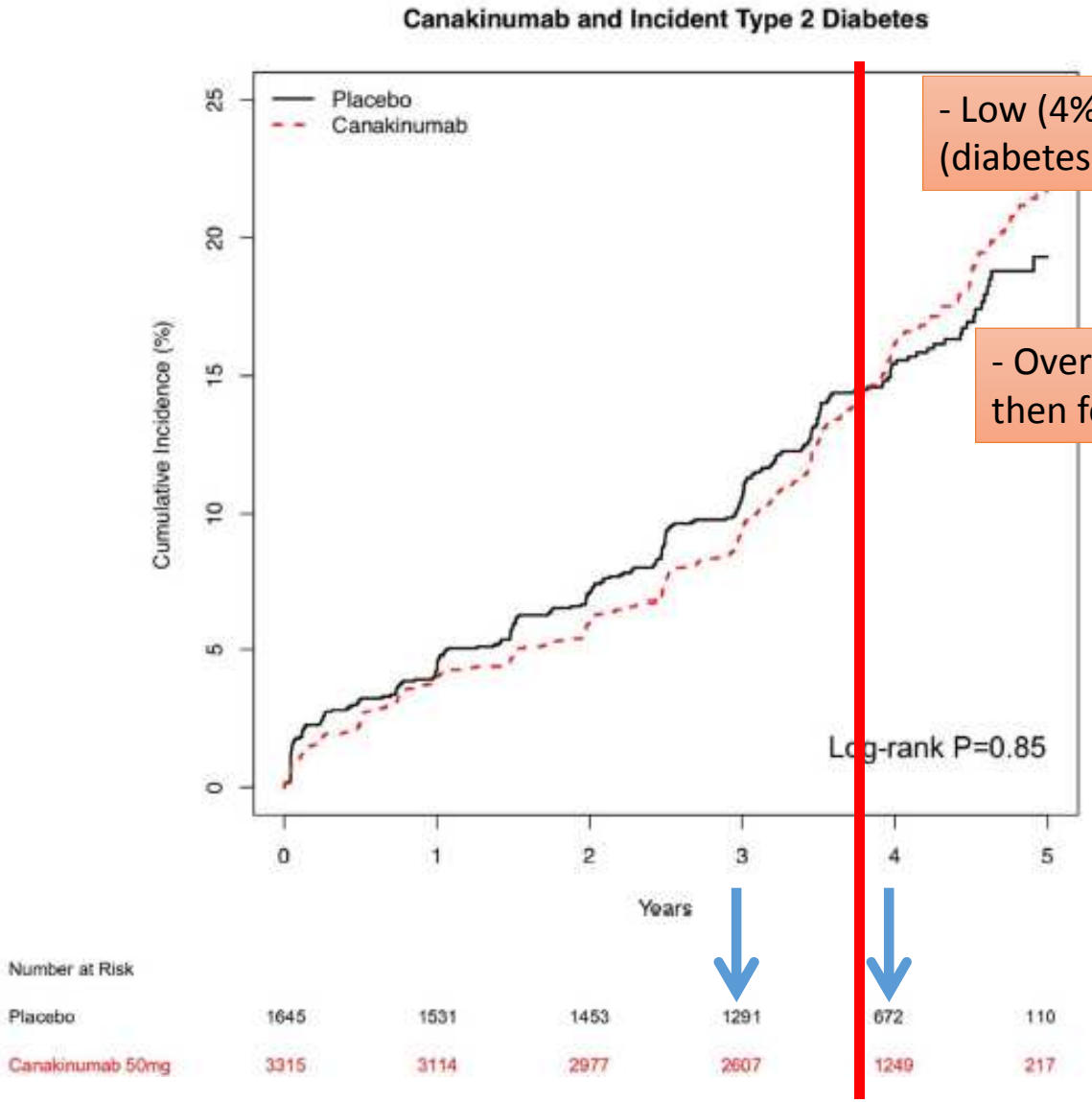
CANTOS: Additional Outcomes (per 100 person years of exposure)

		Canakinumab SC q 3 months			
Adverse Event	Placebo (N=3347)	50 mg (N=2170)	150 mg (N=2284)	300 mg (N=2263)	P-trend
Any SAE	12.0	11.4	11.7	12.3	0.43
Leukopenia	0.24	0.30	0.37	0.52	0.002
Any infection	2.86	3.03	3.13	3.25	0.12
Fatal infection	0.18	0.31	0.28	0.34	0.09/0.02*
Injection site reaction	0.23	0.27	0.28	0.30	0.49
Any Malignancy	1.88	1.85	1.69	1.72	0.31
Fatal Malignancy	0.64	0.55	0.50	0.31	0.0007
Arthritis	3.32	2.15	2.17	2.47	0.002
Osteoarthritis	1.67	1.21	1.12	1.30	0.04
Gout	0.80	0.43	0.35	0.37	0.0001
ALT > 3x normal	1.4	1.9	1.9	2.0	0.19
Bilirubin > 2x normal	0.8	1.0	0.7	0.7	0.34

* P-value for combined canakinumab doses vs placebo

Ridker ESC 2017

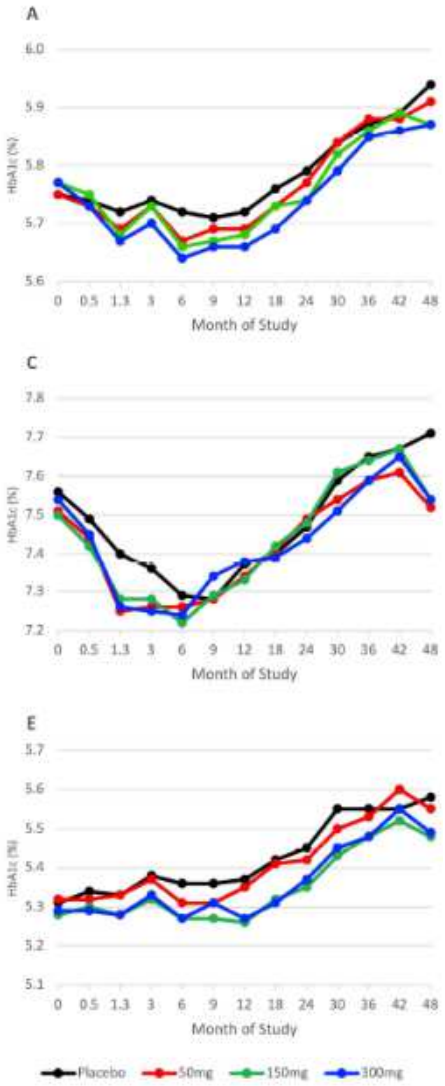
Incident of Diabetes in CANTOS



- Low (4%) conversion rate to diabetes (diabetes prevention program: 25%)

- Over 4 y successful prevention, then follow up loss & loss of effect

HbA1c in CANTOS



Baseline HbA1c 7.1%
(target HbA1c for this patient population : <8)

Magnitude of the effects depends on baseline HbA1c

-During the first months, “pure” anti-Il-1 effect, before drug alteration.

Similar pattern observed in Studies with similar design using DPP-4 inhibitors:

SAVOR, at 2.9 years:
Placebo 7.9; Saxagliptin 7.7%

TECOS, at 48 Months:
Placebo 7.3; Sitagliptin 7.2%

Anti-IL-1β Treatment in patient with a metabolic syndrome

- Cardiovascular complications ↓

(never shown for DPP-IV inhibitors)

- Glycaemia ↓
- Gout ↓
- Arthritis ↓
- Cancer mortality ↓
- Convenient (injection every 3 month)
- Safe: no hypoglycaemia (Cave: severe infections)
- Possible additional effects:
  - renal protection
  - eye protection
  - NASH prevention