Lessons learned from Clinical Programs to Assess Disease Progression: Canakinumab Case Study

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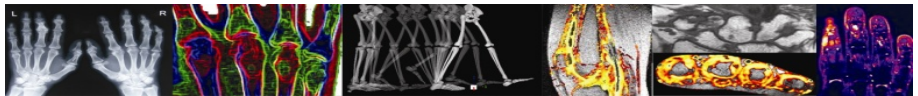
Disclosures

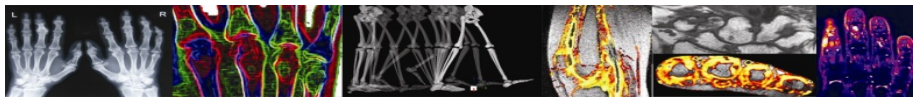
Consultancies or speakers bureaus for:

AbbVie, AstraZeneca, BMS, EMD Serono, Eli Lilly, Flexion, Galapagos, Gilead, Novartis, Pfizer, Regeneron

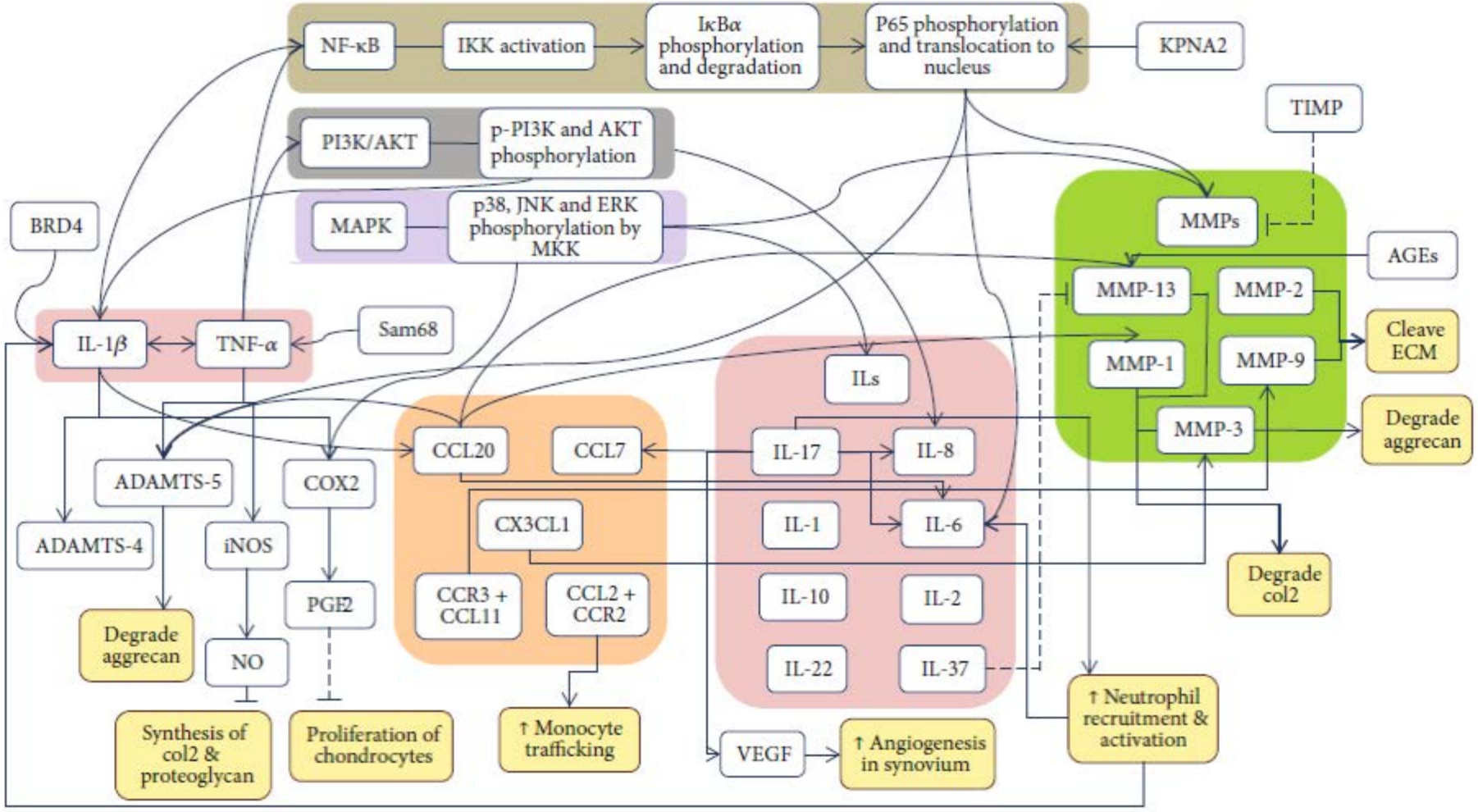


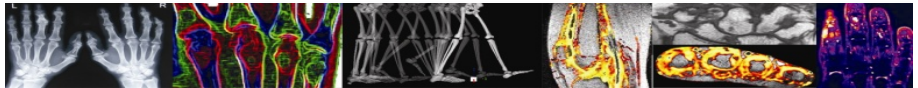
This presentation

- The history of IL-1 inhibition in OA clinical trials
- Considerations from a recent non-OA trial with IL-1 inhibition



IL-1 and OA inflammation





Chow & Chin.
Mediators Inflam 2020

Previous anti-IL1 human knee OA trials

	Anakinra rIL-1Ra *Chevalier, 2009*	**Canakinumab** **Anti-IL-1β Ab** *ACZ885C2201 Study report, ACR 2021*	**AMG108** **IL-1Ra-ab** *Cohen, 2011*	**Lutikizumab (ABT981)** **Anti –IL-1α/β Ab** *Feng, 2017 , Fleischmann, 2019*
N	170, 3 groups	146, 3 groups (Part B)	159 pts (Part B)	347, 4 groups
Design	DB, PC	DB, PC, AC (Naproxen)	DB, PC	DB, PC
Doses	50; 150 mg, 1 dose i.a.	600 mg 1 dose i.a.	300 mg s.c. Q4 wks	25/100/200 mg, s.c.Q2 wks
Duration	12 wks	29 days	12 wks	52 wks
Population	• >18 yrs, OA index knee ACR, pain: >30 mm [VAS] • No active effusion; inflam. NSAID d/c 3 d pre-BSL. Rescue med: acetaminophen <4 mg/ day.	• 40 – 80 yrs, KL gr. 2–3, OA in medial index knee; • Synovitis on MRI or US; • Knee pain 4–8 [NRS-11] for ≥14 of 30 d • BMI<45	• >30 yrs, OA by ACR, radiographic osteophytes, • ≥ 1 of following: age > 50 yrs; morning stiffness ≤ 30 min; crepitus on motion; Knee pain >30 mm [VAS]	• 35 -74 yrs, KL Gr 2 - 3 • BMI 18-34 kg/m^2 • ≥ 1 clinical sign/ symptom active inflammation in index knee • Knee pain 4–8 [NRS11]
Pri…	Total WOMAC Wk 4	VAS, WOMAC pain D 4	1° EP WOMAC pain wk	WOMAC pain wk 16;

The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

The NEW ENGLAND JOURNAL of MEDICINE

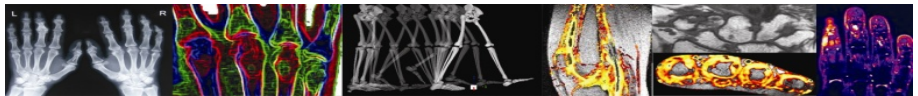
ESTABLISHED IN 1812 SEPTEMBER 21, 2017 VOL. 377 NO. 12

Antiinflammatory Therapy with Canakinumab for Atherosclerotic Disease

P.M. Ridker, B.M. Everett, T. Thuren, J.G. MacFadyen, W.H. Chang, C. Ballantyne, F. Fonseca, J. Nicolau, W. Koenig, S.D. Anker, J.J.P. Kastelein, J.H. Cornel, P. Pais, D. Pella, J. Genest, R. Cifkova, A. Lorenzatti, T. Forster, Z. Kobalava, L. Vida-Simiti, M. Flather, H. Shimokawa, H. Ogawa, M. Dellborg, P.R.F. Rossi, R.P.T. Troquay, P. Libby, and R.J. Glynn, for the CANTOS Trial Group*

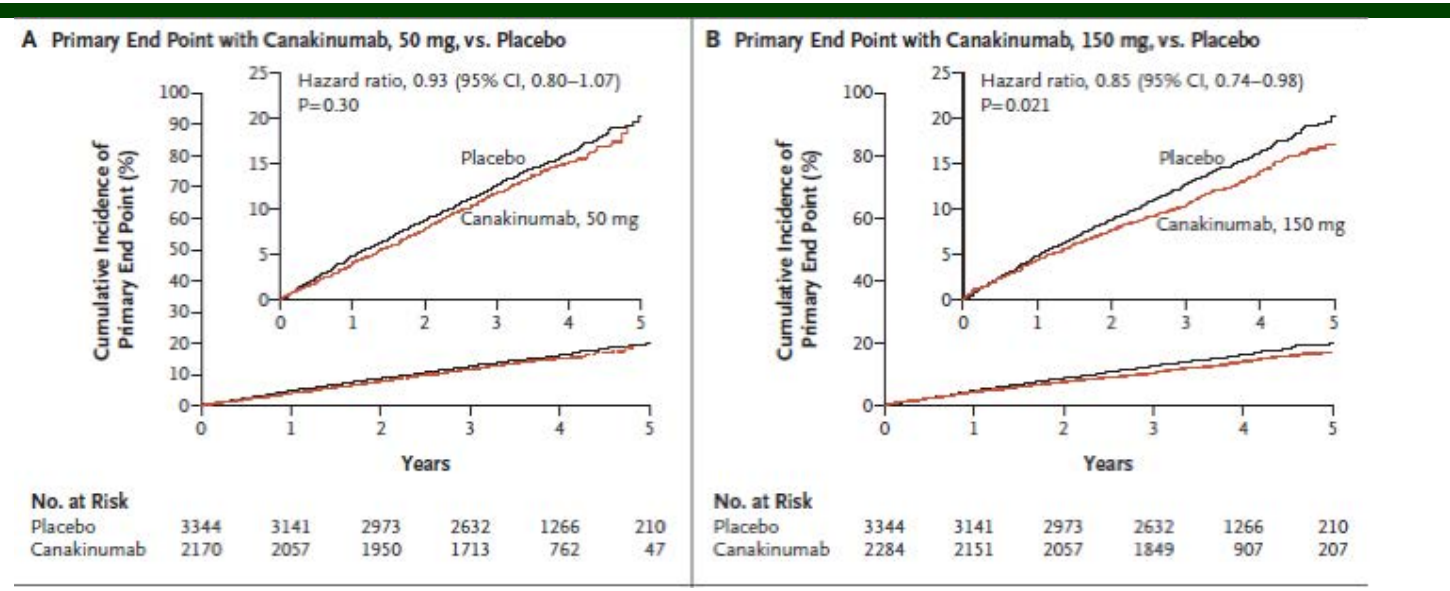
CANTOS main trial

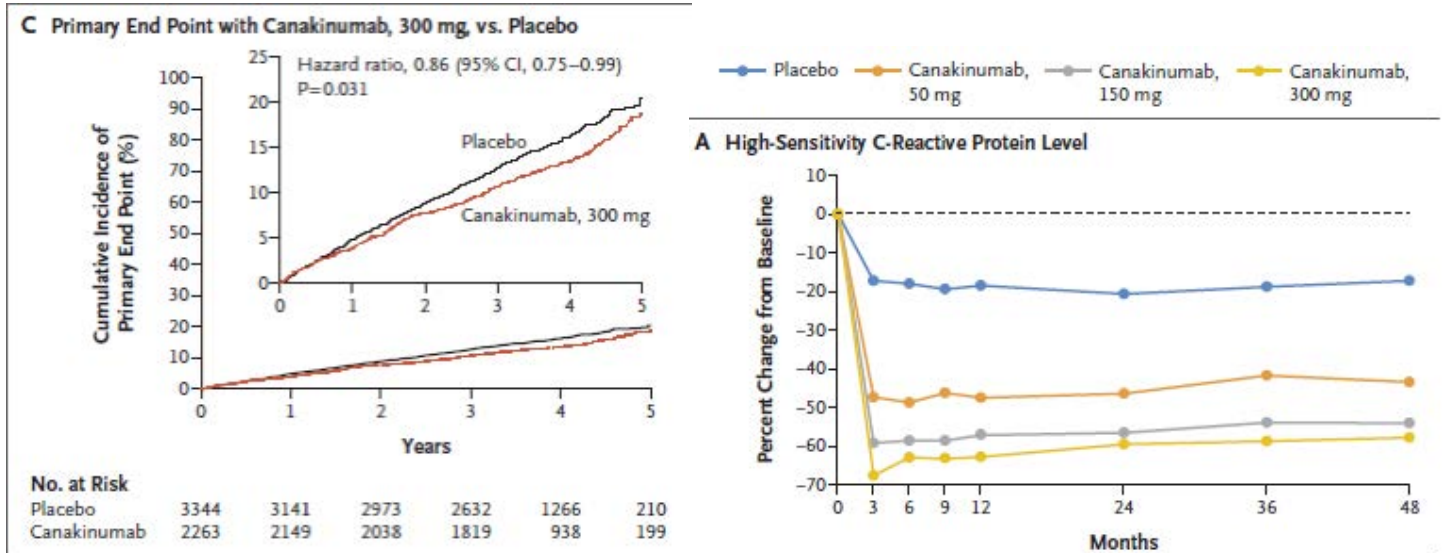
- Hypothesis: treat inflammation underpinning atherothrombosis
- 1091 clinical sites;10,061 men and women with
  - Previous myocardial infarction
  - hsCRP≥2mg/L
- Randomised to canakinumab 50/150/300mg or placebo, s/c every 3 months
- Primary outcome: nonfatal myocardial infarction, nonfatal stroke, cardiovascular death



Ridker PM et al.
N Engl J Med 2017

CANTOS main trial: Results





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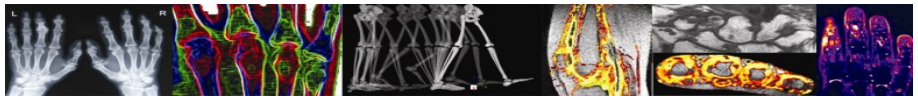
CANTOS main trial: Results (2)

Adverse Event or Laboratory Variable	Placebo Group (N=3344)	Canakinumab	P Value	
		All Doses (N=6717)	For Trend across Doses vs. Placebo	For Combined Dose Groups vs. Placebo
Event — incidence rate per 100 person-yr (no. of patients with event)				
Any serious adverse event	11.96 (1202)	11.82 (2389)	0.43	0.79
Any serious adverse event of infection	2.86 (342)	3.14 (753)	0.12	0.14
Cellulitis	0.24 (30)	0.34 (86)	0.02	0.09
Pneumonia	0.90 (112)	0.95 (238)	0.56	0.62
Urinary tract infection	0.22 (27)	0.21 (52)	0.84	0.87
Opportunistic infection†	0.18 (23)	0.17 (43)	0.97	0.78
Pseudomembranous colitis	0.03 (4)	0.10 (24)	0.13	0.03
Fatal infection or sepsis	0.18 (23)	0.31 (78)	0.09	0.02
Any cancer‡	1.88 (231)	1.75 (431)	0.31	0.38
Fatal cancer‡	0.64 (81)	0.45 (115)	<0.001	0.02
Other adverse event				
Injection-site reaction†	0.23 (29)	0.28 (71)	0.49	0.36
Arthritis	3.32 (385)	2.26 (545)	0.002	<0.001
Osteoarthritis	1.67 (202)	1.21 (298)	0.04	<0.001
Gout	0.80 (99)	0.38 (96)	<0.001	<0.001
Drug-induced liver injury†	0.18 (23)	0.11 (27)	0.004	0.05
Leukopenia	0.24 (30)	0.40 (100)	0.002	0.01
Neutropenia	0.06 (7)	0.10 (25)	0.01	0.17
Any hemorrhage	4.01 (462)	3.78 (877)	0.94	0.31
Thrombocytopenia	0.43 (53)	0.60 (150)	0.02	0.03



Ridker PM et al.
N Engl J Med 2017

Annals of Internal Medicine

ORIGINAL RESEARCH

Effects of Interleukin-1β Inhibition on Incident Hip and Knee Replacement

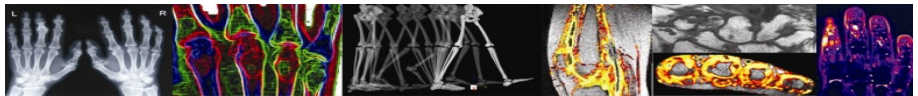
Exploratory Analyses From a Randomized, Double-Blind, Placebo-Controlled Trial

Matthias Schieker, MD*; Philip G. Conaghan, MD*; Linda Mindeholm, MD; Jens Praestgaard, PhD; Daniel H. Solomon, MD; Celeste Scotti, MD; Herman Gram, PhD; Tom Thuren, MD; Ronenn Roubenoff, MD; and Paul M Ridker, MD

CANTOS Exploratory analyses

Post-hoc analysis of CANTOS, looking at

- Time to incident TKR/THR
- Time to first OA-related adverse events
- All cohort and those with prior history of OA
- Median follow-up 3.7yrs
- Median BMI approx. 30; 40% diabetic



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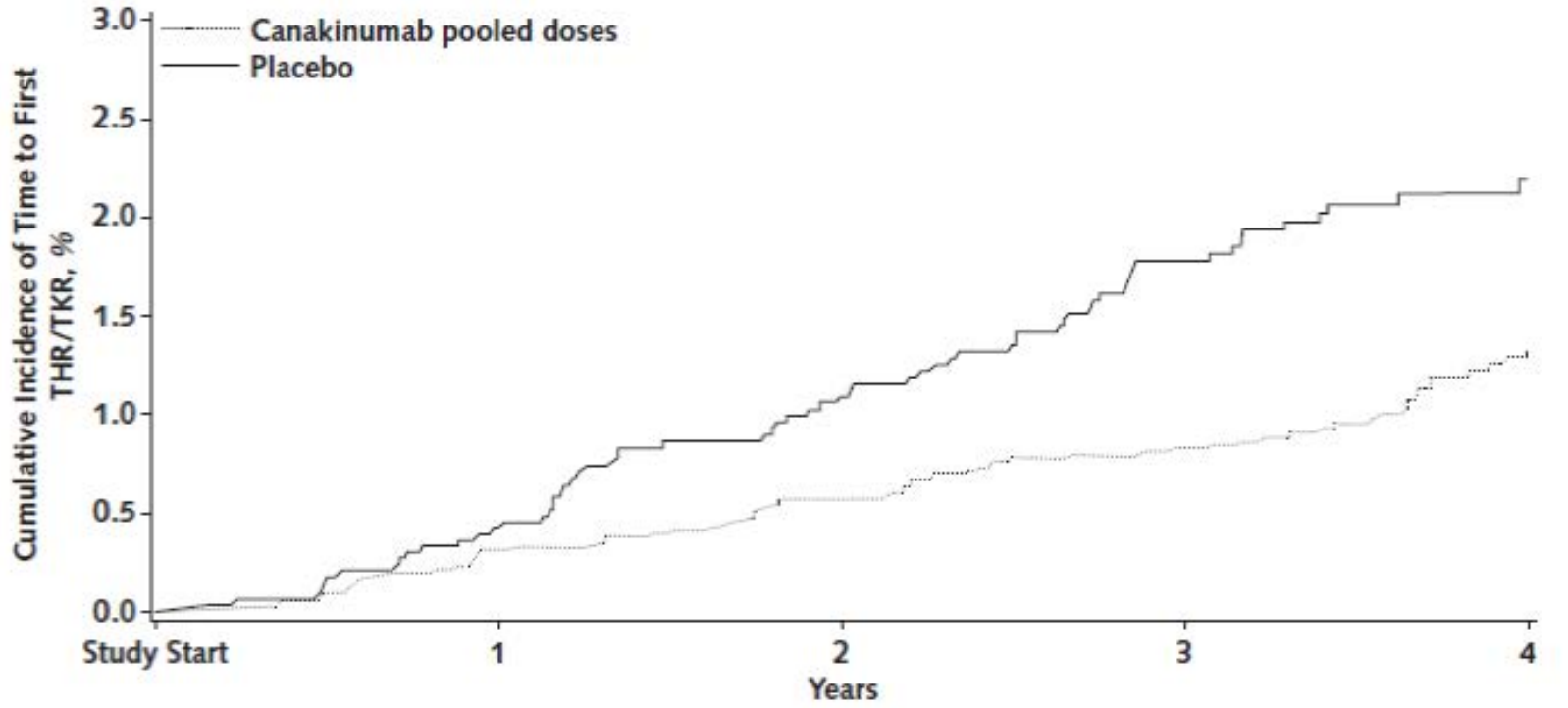
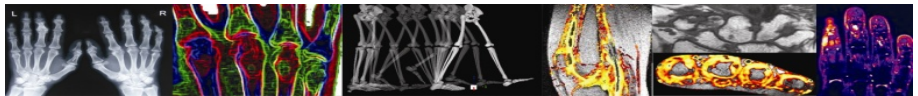
CANTOS Exploratory analyses: Incident THR/TKR



Patients at Risk, *n*					
Pooled doses	6717	6521	6320	5866	2813
Placebo	3344	3241	3129	2819	1397

"..**40% to 50% reductions** in the hazard for incident arthroplasty at all 3 active canakinumab doses."



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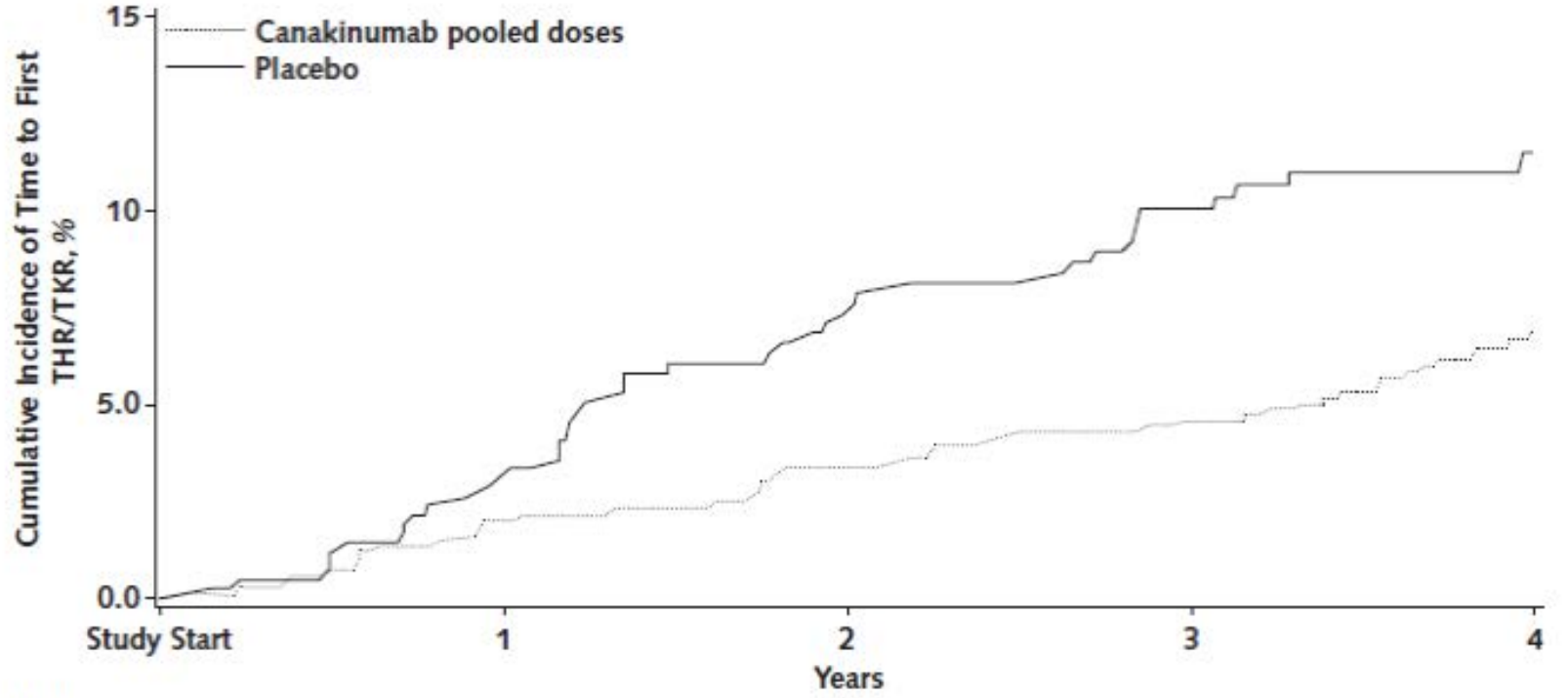
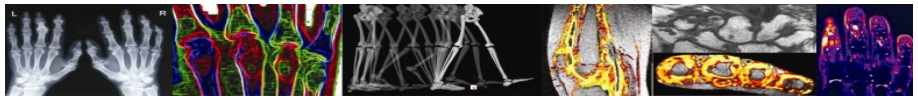
CANTOS Exploratory analyses: Incident THR/TKR in those with baseline OA



Patients at Risk, *n*					
Pooled doses	935	896	854	766	398
Placebo	434	410	383	335	192



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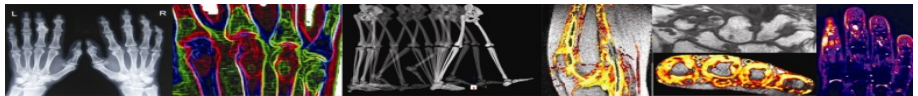
CANTOS Exploratory analyses: Incidence rates and HRs for OA AEs

Trial Cohort/Subgroup	Placebo	Canakinumab			
		50 mg	150 mg	300 mg	All Doses
Full trial cohort, *n*	3344	2170	2284	2263	6717
Osteoarthritis AEs, *n*	203	95	95	109	299
Rate per 100 PY	1.63	1.18	1.08	1.26	1.17
HR (95% CI)	1.00	0.72 (0.56-0.92)	0.68 (0.53-0.86)	0.79 (0.62-0.99)	0.73 (0.61-0.87)
Patients with a history of osteoarthritis at baseline, *n*	434	261	331	343	935
Osteoarthritis AEs, *n*	90	43	42	49	134
Rate per 100 PY	6.02	4.84	3.35	3.85	3.92
HR (95% CI)	1.00	0.80 (0.56-1.15)	0.57 (0.40-0.82)	0.65 (0.46-0.93)	0.66 (0.51-0.87)

AE = adverse event; HR = hazard ratio; PY = person-years.



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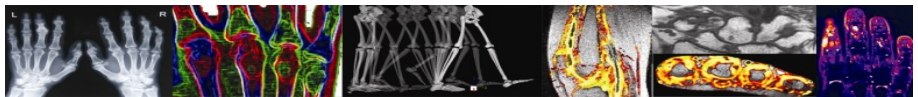
Considerations from CANTOS

- CANTOS data mean a re-think of role of IL-1 and anti-inflammatory pathway inhibition
- Differences with previous trials
  - Inclusion criteria (not an OA trial!)
  - Size of study
  - Duration of treatment
  - TJR as an endpoint



Previous work on virtual TJR endpoint

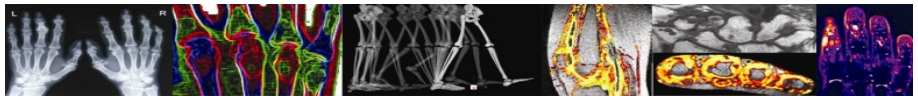
Osteoarthritis and Cartilage

The role of pain and functional impairment in the decision to recommend total joint replacement in hip and knee osteoarthritis: an international cross-sectional study of 1909 patients. Report of the OARSI-OMERACT Task Force on total joint replacement

L. Gossec †*, S. Paternotte †, J.F. Maillefert ‡§ ‖, C. Combescure ¶, P.G. Conaghan #, A
K.-P. Gunther |||, G. Hawker ¶¶##, M. Hochberg †††‡‡‡, J.N. Katz §§§|||||| ¶¶¶, M. Klo
K. Lim ‡‡‡‡, L.S. Lohmander §§§§, N.N. Mahomed ||||||, L. March ¶¶¶¶, K. Pavelka ##
E.M. Roos ‡‡‡‡‡, L. Sanchez-Riera §§§§§, J.A. Singh ||| |||||, M.E. Suarez-Almazor ¶¶¶¶
for the OARSI-OMERACT Task Force "total articular replacement as outcome meas

OARSI/OMERACT Initiative to Define States of Severity and Indication for Joint Replacement in Hip and Knee Osteoarthritis. An OMERACT 10 Special Interest Group

LAURE GOSSEC, SIMON PATERNOTTE, CLIFTON O. BINGHAM III, DANIEL O. CLEGG, PHILIPPE COSTE, PHILIP G. CONAGHAN, AILEEN M. DAVIS, GIAMPAOLO GIACOVELLI, KLAUS-PETER GUNTHER, GILLIAN HAWKER, MARC C. HOCHBERG, JOANNE M. JORDAN, JEFFREY N. KATZ, MARGREET KLOPPENBURG, ARTURO LANZAROTTI, KEITH LIM, L. STEFAN LOHMANDER, NIZAR N. MAHOMED, JEAN FRANCIS MAILLEFERT, REBECCA L. MANNO, LYN M. MARCH, STEVEN A. MAZZUCA, KAREL PAVELKA, LEONARDO PUNZI, EWA M. ROOS, LUCIO C. ROVATI, HELEN SHI, JASVINDER A. SINGH, MARIA E. SUAREZ-ALMAZOR, ELEONORA TAJANA-MESSI, and MAXIME DOUGADOS, For the OARSI-OMERACT Task Force Total Articular Replacement as Outcome Measure in OA



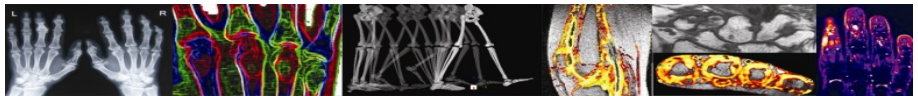
Gossec L et al. Osteoarthritis Cartilage 2011
Gossec L et al. J Rheumatol 2011

Re-considering important OA trial endpoints

- “time to TKR”

  or

- Time to a poor outcome (related to how the patient feels functions or survives): “time to TKR or severe pain or severely impaired functioning”



Kim Y et al.
Arthritis Care Res 2020 online

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- Matthias Schieker, Linda Mindeholm, Jens Praestgaard & the Novartis team