Inflamación y DM: iniciando el daño cardiovascular

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Conflictos de interés

- Conferencista: Astra Zeneca, Abbott Nutrición, Novartis Oncology, Novo Nordisk, Merck Sharp & Dohme, Roche, Glaxo SmithKline, Sanofi Aventis, Bayer, Pfizer, Novartis
- Advisory Board: Novartis Oncology, Sanofi Aventis, Astra Zeneca, Novo Nordisk, Stendhal, Pfizer
- Investigación clínica: Astra Zeneca, Novartis Pharma Logistics Inc., Merck Sharp & Dohme, Glaxo SmithKline, Organon, Boehringer Ingelheim, Roche, Novo Nordisk

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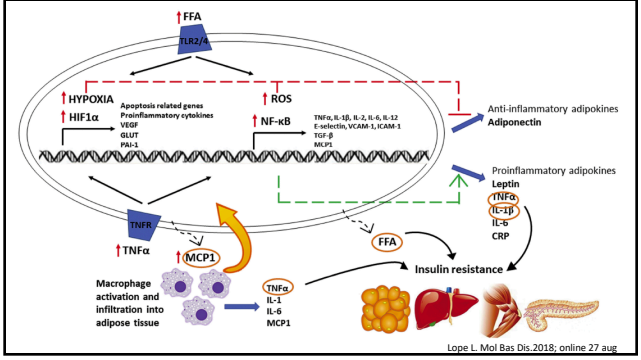
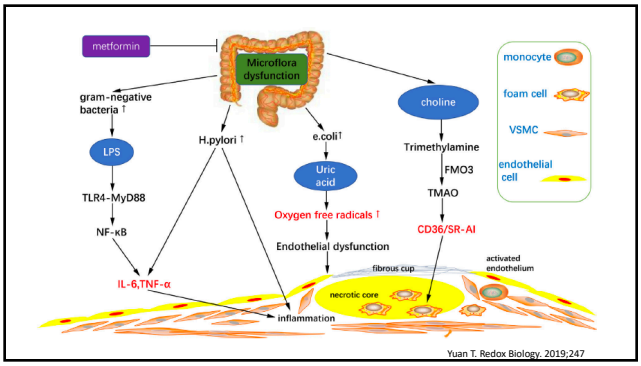
Preguntas a discutir:

- Controlar la inflamación… previene diabetes?
- Controlar inflamación… puede reducir Hba1c?
- Reducir inflamación puede conferir protección de lesión de órgano blanco?
- Controlar inflamación como tal, puede reducir eventos vasculares en diabetes?



Lope L. Mol Bas Dis.2018; online 27 aug



Yuan T. Redox Biology. 2019;247

Tejido adiposo

- Libera adipoquinas
- Leptina estimula secreción de TNF
- Resistina induce liberación de citoquinas inflamatorias
- Tejido adiposo también secreta citoquinas que estimulan secreción de CRP por el hígado

Lope L. Mol Bas Dis.2018; online 27 aug

Hígado

- Citoquinas y adipoquinas pueden producir activación e infiltración de células de Kupffer

Lope L. Mol Bas Dis.2018; online 27 aug

Cerebro

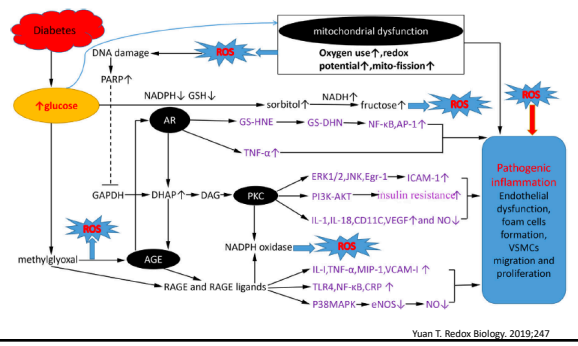
- Obesidad induce vías inflamatorias en hipotálamo lo que lleva a apoptosis de células hipotalámicas
- Desregulación de homeostasis energética
- Cierta asociación entre obesidad y esclerosis multiple
  - Restricción calórica podría proveer beneficios

Lope L. Mol Bas Dis.2018; online 27 aug

Páncreas

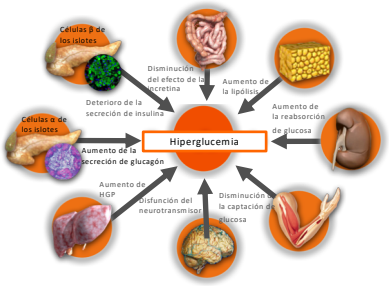
- Ácidos grasos inducen inflamación en islotes
  - Saturados, como ácido palmítico llevan a fallo de células beta
  - Insaturados, como ácido oleico, tienen efecto protector, con menos apoptosis de células beta
- Citoquinas inflamatorias producen destrucción y desdiferenciación de las células beta
  - El más importante es el IL-1 beta
  - Hiperglicemia como tal induce liberación de IL-1 beta
  - Glucotoxicidad y lipotoxicidad

Lope L. Mol Bas Dis.2018; online 27 aug

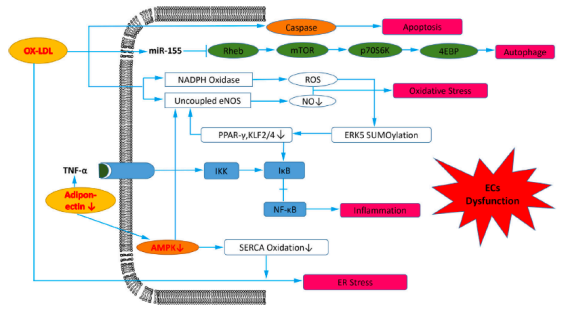


Yuan T. Redox Biology. 2019;247

El octeto ominoso



Impacto de inflamación en riesgo CV



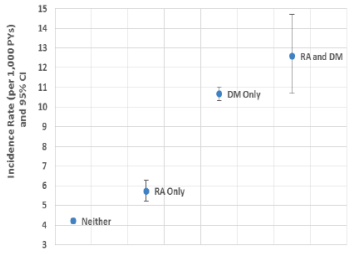
Yuan T. Redox Biology. 2019;247

Recomendaciones EULAR 2016

Recommendations			
1. Disease activity should be controlled optimally in order to lower CVD risk in all patients with RA, AS or PsA	2b-3	B	9.1 (1.3)
2. CVD risk assessment is recommended for all patients with RA, AS or PsA at least once every 5 years and should be reconsidered following major changes in antirheumatic therapy	3–4	C	8.8 (1.1)
3. CVD risk estimation for patients with RA, AS or PsA should be performed according to national guidelines and the SCORE CVD risk prediction model should be used if no national guideline is available	3–4	C–D	8.7 (2.1)
4. TC and HDLc should be used in CVD risk assessment in RA, AS and PsA and lipids should ideally be measured when disease activity is stable or in remission. Non-fasting lipids measurements are also perfectly acceptable	3	C	8.8 (1.2)
5. CVD risk prediction models should be adapted for patients with RA by a 1.5 multiplication factor, if this is not already included in the model	3–4	C	7.5 (2.2)
6. Screening for asymptomatic atherosclerotic plaques by use of carotid ultrasound may be considered as part of the CVD risk evaluation in patients with RA	3–4	C–D	5.7 (3.9)
7. Lifestyle recommendations should emphasise the benefits of a healthy diet, regular exercise and smoking cessation for all patients	3	C	9.8 (0.3)
8. CVD risk management should be carried out according to national guidelines in RA, AS or PsA, antihypertensives and statins may be used as in the general population	3–4	C–D	9.2 (1.3)
9. Prescription of NSAIDs in RA and PsA should be with caution, especially for patients with documented CVD or in the presence of CVD risk factors	2a-3	C	8.9 (2.1)
10. Corticosteroids: for prolonged treatment, the glucocorticoid dosage should be kept to a minimum and a glucocorticoid taper should be attempted in case of remission or low disease activity; the reasons to continue glucocorticoid therapy should be regularly checked	3–4	C	9.5 (0.7)

Agca R. Ann Rheum Dis. 2017;76:17-28

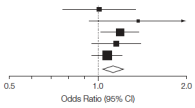
AR es equivalente a DM en riesgo CV?



Curtis JR. Arthritis Care Res. 2018 Feb 6 doi: 10.1002/acr.23535

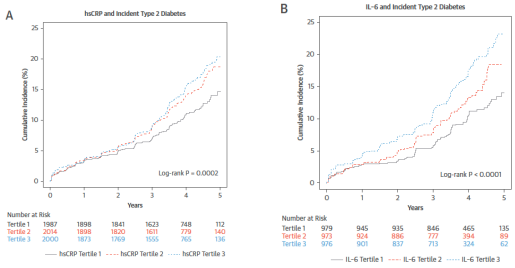
Dosis de estatina

Incident Diabetes	Cases/Total, No. (%) Intensive Dose	Cases/Total, No. (%) Moderate Dose	OR (95% CI)
PROVE IT–TIMI 22,[18] 2004	101/1707 (5.9)	99/1688 (5.9)	1.01 (0.76-1.34)
A to Z,[17] 2004	65/1768 (3.7)	47/1736 (2.7)	1.37 (0.94-2.01)
TNT,[15] 2005	418/3798 (11.0)	358/3797 (9.4)	1.19 (1.02-1.38)
IDEAL,[16] 2005	240/3737 (6.4)	209/3724 (5.6)	1.15 (0.95-1.40)
SEARCH,[8] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	1449/16408 (8.8)	1300/16344 (8.0)	1.12 (1.04-1.22)
Heterogeneity: $I^2 = 0\%$; $P = .60$			



Preiss D. JAMA. 2011;305:2556

CANTOS y aparición de DM



Everett. J Am Coll Cardiol. 2018;71:2392

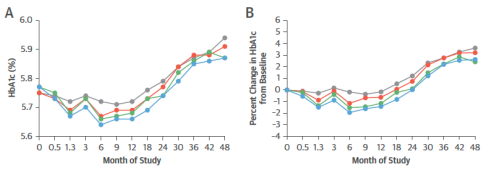
Canakinumb y aparición de DM

	Placebo	Canakinumab Dose 50 mg	150 mg	300 mg	All Doses Combined
Adjudicated new-onset diabetes					
N events/N at risk	246/1,645	161/1,089	171/1,094	169/1,132	501/3,315
Incidence rate*	4.20	4.24	4.35	4.12	4.23
Hazard ratio (95% CI)	–	1.04 (0.85–1.27)	1.03 (0.85–1.26)	0.98 (0.80–1.19)	1.01 (0.87–1.18)
p value†	–	0.70	0.75	0.80	0.86
All physician-reported diabetes					
N events/N at risk	279/1,645	186/1,089	191/1,094	190/1,132	567/3,315
Incidence rate*	4.84	4.97	4.92	4.68	4.85
Hazard ratio (95% CI)	–	1.06 (0.88–1.27)	1.02 (0.84–1.22)	0.97 (0.80–1.16)	1.01 (0.88–1.17)
p value†	–	0.56	0.88	0.70	0.89

New-onset type 2 diabetes diagnosis is the protocol pre-specified secondary endpoint and was centrally adjudicated. The rates of all physician-reported new-onset diabetes in patients with pre-diabetes at baseline are also presented. *Incidence rate per 100 person-years of observation. †p value for canakinumab vs. placebo comparison.
CI = confidence interval.

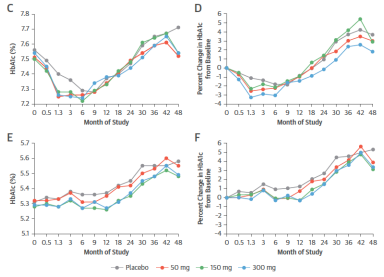
Everett. J Am Coll Cardiol. 2018;71:2392

CANTOS: evolución de Hba1c en DM



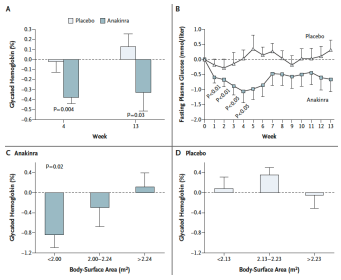
Everett. J Am Coll Cardiol. 2018;71:2392

CANTOS: evolución de Hba1c en no DM



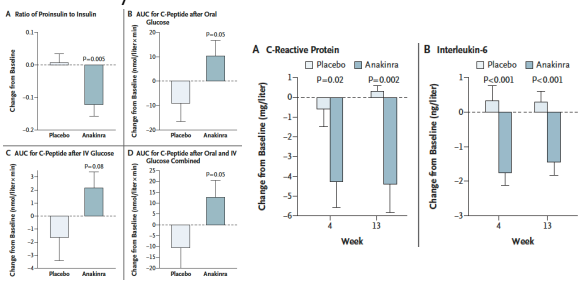
Everett. J Am Coll Cardiol. 2018;71:2392

Anakinra en DM



Larsen CM. N Engl J Med. 2007;356:1517

Anakinra y función de células beta



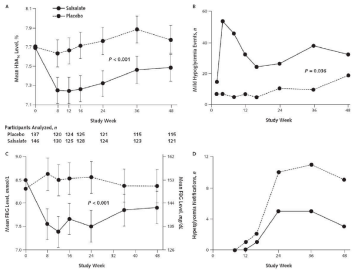
Larsen CM. N Engl J Med. 2007;356:1517

Salicilatos

- No contienen acetil por lo que no puede inhibir COX
- Salsalato o trilisato son prodrogas de salicilatos
- TINSAL-T2D

Goldfine AB. Ann Inter Med. 2013:159:1

TINSAL-T2D



Goldfine AB. Ann Inter Med. 2013:159:1

Efecto de antidiabéticos

Antidiabéticos e inflamación

Antidiabetic agents	Anti-inflammatory effects	Reno-protective effects
Insulin	Prevents ICAM-1, MCP-1, TNF-α, NF-κb, and TLRs expression, and induces NO release	No verified effects
Biguanides	Suppress inflammation by inhibition of oxidative stress, IL-1β, TNF-α, MMP-9, COX-2, IL-10, NF-κb, and rise in NO bioavailability; decrease the neutrophil to lymphocyte ratio	Ameliorate renal injury by AMPK activation; prevent kidney injuries in diabetic animals by downregulation of TNF-α, TGF-β, collagen type-1a, and IL-1β
Sulfonylureas	Prevent inflammatory responses by MAPKs/NF-κb-dependent pathway; suppress Th2 cytokines, VCAM-1, p-STAT6, TNF-α, NF-κb, caspase-3, PGE2, and IL-10 expressions; inhibit NLRP3 inflammasome; ameliorate oxidative stress	No verified effects
Thiazolidinediones	Prevent macrophage activation; reduce expression of CRP, MMP-9, ICAM-1, PAI-1, IL-1, and IL-6	Prevent NF-κb activation and macrophage infiltration; down-regulate IL-6, CRP, MMP-9, and TNF-α in renal mesangial cells; ameliorate inflammation in renal tubular epithelial cells via NF-κb inhibition
DPP-4 inhibitors/GLP-1 receptor agonists	Prevent; adipocyte and hepatocyte inflammation	Inhibit the inflammatory cytokine expression through NF-κb inhibition in renal glomeruli
Alpha glucosidase inhibitors	Reduce ICAM-1, VCAM-1, IL-6, IL-1β, TNF-α, and CRP expression	No verified effects
SGLT2i	Downregulate MCP-1, TGF-1β, IL-6, TNF-α, and CRP expression	Prevent p65 and TLR4 activity; down-regulate MCP-1, ICAM-1, PAI-1, TGF-β, type-4 collagen, and OPN expression, CD68 macrophage accumulation
Meglitinides	No verified effects	No verified effects

Yarjbeygi H. J Cell Physiol. 2018; online oct 15

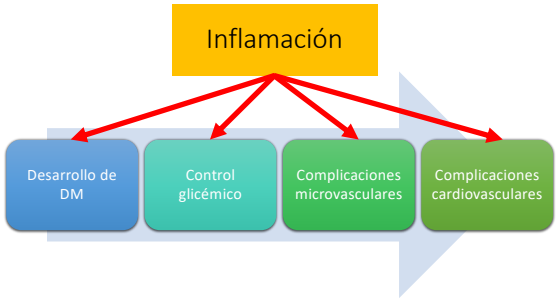
iSGLT-2

Changes in serum inflammatory markers with the three worldwide commercially available SGLT2 inhibitors in patients with type 2 diabetes

References	Glifozin	Leptin	Adiponectin	hsCRP	TNF-α	IL-6	IFN-γ
Ferrannini et al., 2010 [21]	Dapa	NA	NA	↓	NA	NA	NA
Bailey et al., 2012 [18]	Dapa	↓	↑	NA	NA	NA	NA
Okamoto et al., 2016 [22]	Dapa	NA	↑*	↓*	NA	NA	NA
Matsumura et al., 2017 [19]	Cana	NA	↑*	NA	↓	NA	NA
Hattori, 2017 [23]	Empa	NA	NA	↓	NA	NA	NA
Tobita et al., 2017 [24]	Dapa	NA	↑*	↓	NA	NA	NA
Sato et al., 2018 [25]	Dapa	NA	NA	NA	↓*	NA	NA
Garvey et al., 2018 [20]	Cana	↓	↑	↓	↑, ↓	NA	NA
Tan and Tan, 2018 [26]	Empa	NA	NA	NA	↓*	↓*	↓*

These are numerical trends except where * ($P < 0.05$) indicates significant changes.
hsCRP: high-sensitivity C-reactive protein; TNF-α: tumour necrosis factor-alpha; IL-6: interleukin-6; IFN-γ: interferon-gamma; Dapa: dapagliflozin; NA: not available; Cana: canagliflozin; Empa: empagliflozin.

Bonnet F. Diab Metab. 2018;



Inflamación y neuropatía

- Múltiples estudios bloqueando productos avanzados de glicosilación no han sido efectivos
- Modular inflamación no ha sido exitoso en manejo de neuropatía

Inflamación y nefropatía

- Macrófagos infiltran riñon
  - Ciclo de liberación de citoquinas y reclutamiento de monocitos y macrófagos
  - Cambios estructurales relacionados a inflamación
  - Infiltración y degranulación por mastocitos
  - Correlacionan con la pérdida de función renal

Perez-Morales RE. Nephron. 2018; online oct 1.

Inflamación y nefropatía diabética

Drug	Target	Identifier	Study population	Outcomes
Pentoxifylline	Inflammatory Cytokines	EudraCT number 2007-005985-10	Type 2 diabetes eGFR 15–60 UAE >30 mg/24 h	Mean difference in UAE of 21% ($p < 0.001$) and eGFR decline 4.3 mL/min/1.73 m^2 lower than in the placebo group ($p < 0.001$)
Baricitinib	JAK1/JAK2	NCT01683409	Type 2 diabetes Macroalbuminuria eGFR 20–75 mL/min/1.73 m^2	Albuminuria reduction by 40% No effect on eGFR
Emanticap Pegol (NOX-E36)	CCL2	NCT01547897	Type 2 diabetes eGFR >25 mL/min/1.73 m^2 UACR >100 mg/g	Albuminuria reduction by 29% compared with baseline ($p < 0.05$), but no significant difference with placebo
CCX 140-B	CCR2	NCT01447147	Type 2 diabetes eGFR ≥25 mL/min/1.73 m^2 UACR 100–3,000 mg/g	18% reduction of albuminuria compared with placebo ($p < 0.0004$) in the 5 mg group. No reduction of albuminuria in the 10 mg group
CTP-499	PDE	NCT01487109	Type 2 diabetes eGFR no limit UACR 300–5,000 mg/g	16% UACR reduction
LY3016859	TGF-a/epiregulin	NCT01774981	eGFR <90 mL/min/1.73 m^2 UACR >400 mg/g	Study ongoing. No results available

eGFR, estimated glomerular filtration rate; TGF-a, transforming growth factor alpha; UACR, urinary albumin-to-creatinine ratio.

Perez-Morales RE. Nephron. 2018; online oct 1.

PREDIAN: pentoxifilina

Variable	Control Group	PTF Group	*P* Value between Groups
eGFR (ml/min/1.73 m^2)			
Mean baseline±SD	37.6±11.9	37.1±12.4	
Least-square mean change± SEM (95% CI) per follow-up period			
6 mo	−1.7±0.1 (−2.1 to −1.4)	−1.4±0.1 (−1.7 to −1.0)	0.1
12 mo	−3.4±0.3 (−4.1 to −2.8)	−1.2±0.3 (−1.9 to -0.6)	<0.001
18 mo	−5.3±0.3 (−6.1 to −4.5)	−1.7±0.4 (−2.5 to -0.9)	<0.0001
24 mo	−6.5±0.4 (−7.3 to −5.6)	−2.1±0.4 (−3.0 to -1.2)	<0.0001
UAE			
Median baseline (IQR) (mg/d)	1000 (600–1800)	1100 (689–2190)	
Least-square mean percentage change per follow-up period±SEM (95% CI)			
6 mo	1.4±1.1 (−0.8 to 3.8)	−10.6±1.2 (−13.0 to -8.2)	<0.001
12 mo	4.9±2.8 (−0.7 to 10.6)	−13.0±2.9 (−18.8 to −7.2)	<0.0001
18 mo	4.9±2.6 (−0.3 to 10.1)	−14.8±2.7 (−20.1 to −9.4)	<0.0001
24 mo	5.7±2.7 (−0.3 to 11.1)	−14.9±2.7 (−20.4 to −9.4)	<0.0001
Patients per follow-up period (*n*)			
6 mo	87	81	
12 mo	85	81	
18 mo	84	79	
24 mo	82	78	

Navarro-Gonzalez JF. J Am Soc Nephrol. 2015;26:220

PREDIAN: pentoxifilina

Adverse Events	Control Group (*n*=87)	PTF Group (*n*=82)	*P* Value
Hospitalization episodes	32 (36.7)	24 (29.2)	0.29
Cardiovascular events			
Myocardial infarction	2 (2.3)	1 (1.2)	0.59
Stroke	2 (2.3)	1 (1.2)	0.59
Heart failure	4 (4.5)	3 (3.6)	0.75
Revascularization	5 (5.7)	2 (2.4)	0.28
Syncope	1 (1.1)	0	
Noncardiovascular events			
ESRD	3 (5.7)	2 (2.4)	0.60
AKI	4 (4.5)	5 (6.0)	0.31
Digestive symptoms	9 (10.3)	18 (21.9)	0.03
Hemorrhoid bleed	2 (2.3)	1 (1.2)	0.59
Pneumonia	1 (1.1)	2 (2.4)	0.52
Eye disorders	3 (5.7)	3 (3.6)	0.94
Malignant neoplasms	1 (1.1)	0	

Unless otherwise noted, values are expressed as the number (percentage) of patients. Revascularization indicates peripheral and cardiac angioplasty, and cardiac bypass procedures.

Navarro-Gonzalez JF. J Am Soc Nephrol. 2015;26:220

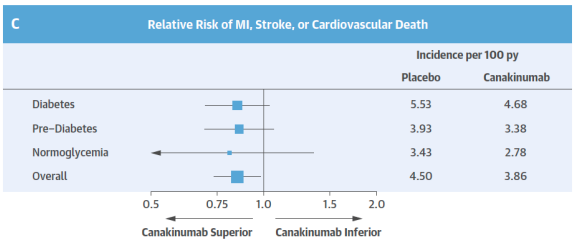
hSCRP en CARDS

CVD event (*N*=2,258)	Events/persons	Event rate (per 100 person-years)	Adjusted HR[a] (95% CI)
Major cardiovascular event			
Placebo	74/1,115	2.33	1
Atorvastatin subgroups			
LDL-c <1.8 mmol/l, CRP <19.0 nmol/l	14/400	1.14	0.44 (0.25, 0.78)
LDL-c <1.8 mmol/l, CRP ≥19.0 nmol/l	16/352	1.59	0.69 (0.40, 1.19)
LDL-c ≥1.8 mmol/l, CRP <19.0 nmol/l	5/177	0.98	0.47 (0.19, 1.16)
LDL-c ≥1.8 mmol/l, CRP ≥19.0 nmol/l	7/214	1.24	0.68 (0.31, 1.47)
Any cardiovascular event			
Placebo	116/1,115	3.73	1
Atorvastatin subgroups			
LDL-c <1.8 mmol/l, CRP <19.0 nmol/l	24/400	1.99	0.55 (0.35, 0.86)
LDL-c <1.8 mmol/l, CRP ≥19.0 nmol/l	28/352	2.84	0.73 (0.48, 1.12)
LDL-c ≥1.8 mmol/l, CRP <19.0 nmol/l	7/177	1.38	0.41 (0.19, 0.89)
LDL-c ≥1.8 mmol/l, CRP ≥19.0 nmol/l	15/214	2.72	0.69 (0.39, 1.23)

[a] Adjusted for age, sex, baseline LDL-cholesterol, baseline CRP, race, smoking status, systolic blood pressure, BMI and HbA_{1c}

LDL-c, LDL-cholesterol

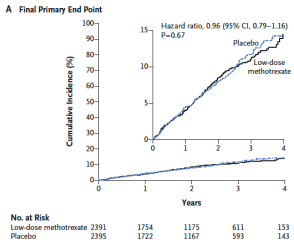
CANTOS: desenlaces según status glicémico



Everett, B.M. et al. J Am Coll Cardiol. 2018;71(21):2392–401.

Everett, J Am Coll Cardiol. 2018;71:2392

CIRT: metotrexate dosis bajas



- Mediana edad 65.6 años
- 33% diabetes
- 32.2% síndrome metabólico
- Población en prevención primaria de alto riesgo y prevención secundaria
- hsCRP medio 1.53 mg/L

Ridker PM. N Engl J Med. 2018; online Dec 3

Conclusiones

- Hay una relación bidireccional entre diabetes e inflamación
- Pacientes con mayores niveles de marcadores inflamatorios hacen más DM
- Control de inflamación puede tener impacto en control glicémico
- Muchos antidiabéticos tienen propiedades antiinflamatorias
- Bajar inflamación en diabéticos reduce eventos cardiovasculares
- Bajar inflamación puede tener impacto en nefropatía diabética

Preguntas…

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Puede descargar la presentación en:

www.EndoDrChen.com