ACC Latin America Conference 2017

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JUNE 22 – 24, 2017

GLOBAL EXPERTS, LOCAL LEARNING

In Search of Truth: Identifying Bias-Spin and Applying Research to My Patient

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Disclosure

No Tengo Conflicto de Interés

María

Decisiones

Lo Fundamental en Medicna y en MBE es...

Entre mejor sea la calidad de la investigación mayor confianza en la toma de la decisión. **"Continuum"**

Tomar una **decisión** clínica en base a **la mejor evidencia disponible**

Lo Fundamental aquí (MBE) es...

Entre mejor sea la calidad de la investigación mayor confianza en la toma de la decisión. **"Continuum"**

La evidencia por si misma **NUNCA** es suficiente para tomar una decisión clínica.

Modelo de Medicina Basada en Evidencia

Corrupción en la Evidencia

Sistematicamente las preferencias de los pacientes son ignoradas

Final de la MBE?

BIAS

[Sesgo(s)]

¿El Azar (Chance-Random Error) o Bias (Error Sistemático?

BIAS

Sesgo (Bias) en RCTs

Aleatorización

Encubrimiento de la secuencia (Concelement)

Ciego*

Pérdida de Pacientes (Follow-up)

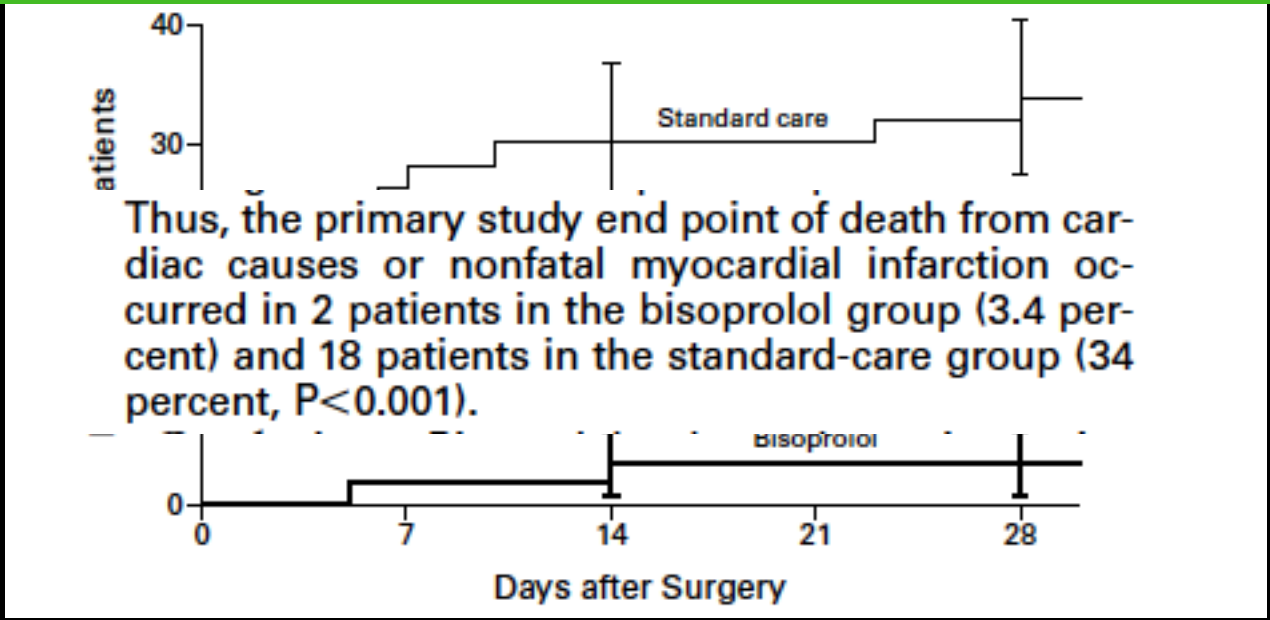
Ensayo truncado por hallazgo beneficioso

Intention-to-treat Analysis

BIAS

- RCT Bisoprolol vs Placebo (Perioperativo)
- Eco Cardio + Dobutamina + = Cirugía Vascular
- 173 Pacientes

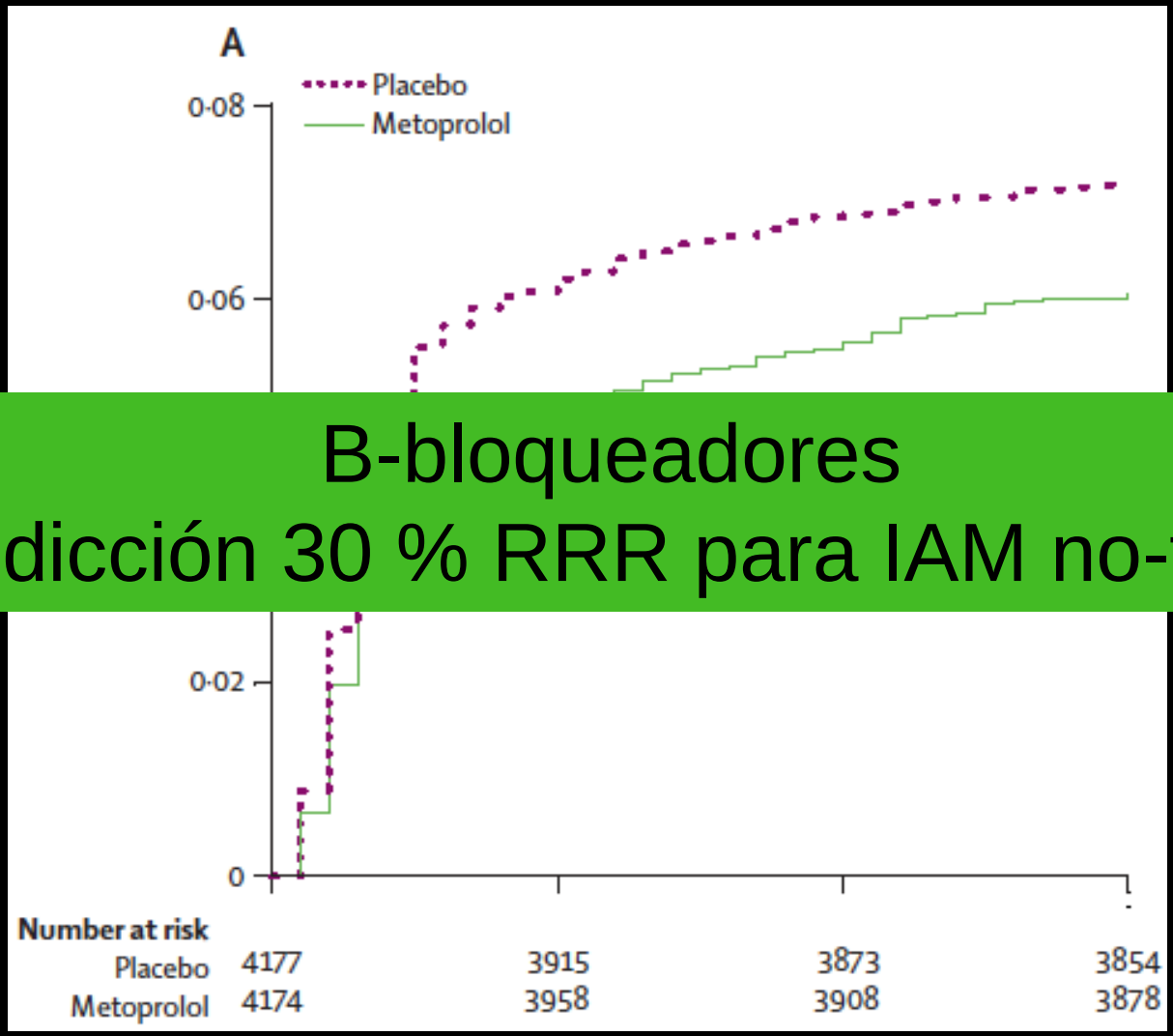
100 % RRR para IAM no-fatal
80% RRR para Muerte cardiovascular



Polderman et al. NEJM 2002

BIAS

POISE Trial

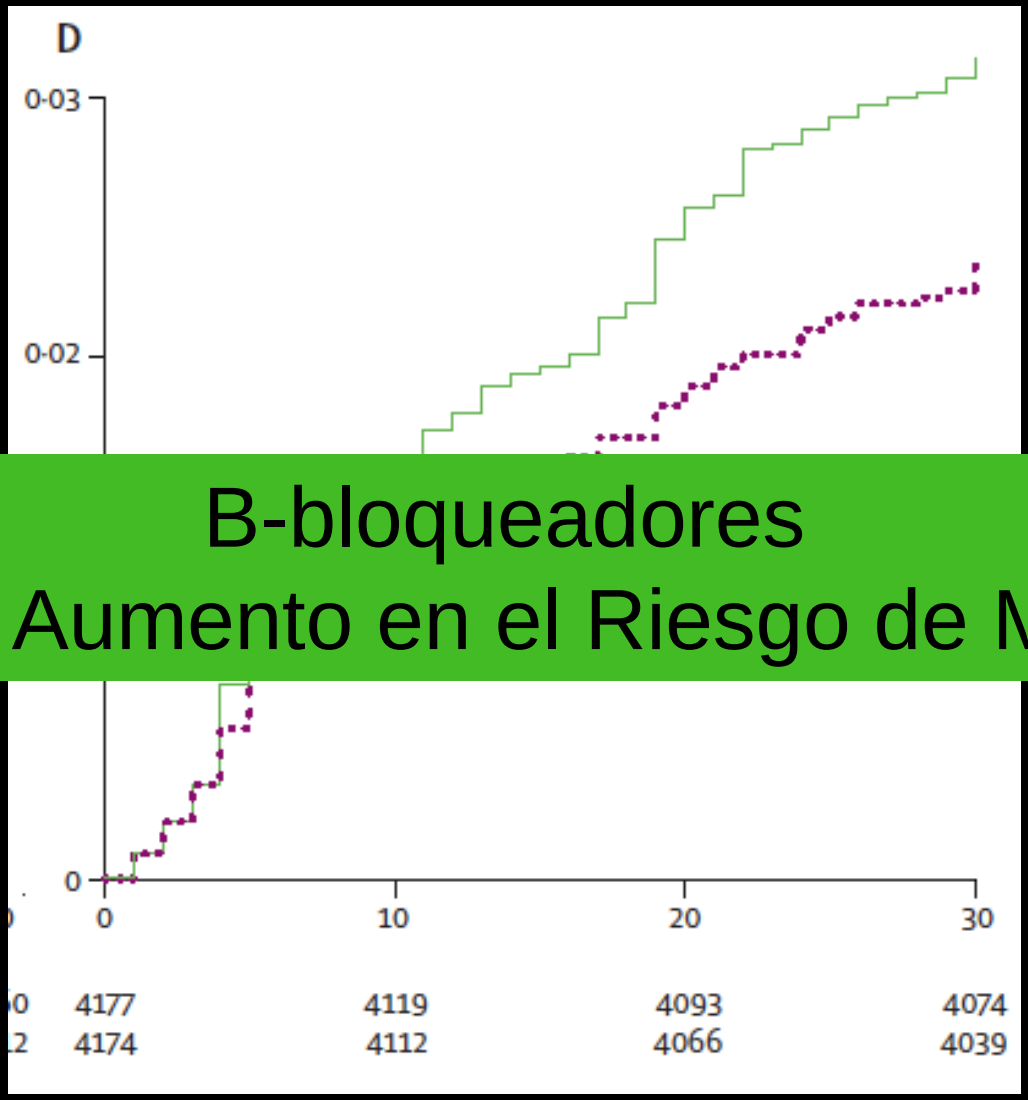


B-bloqueadores
Redicción 30 % RRR para IAM no-fatal

Bernard et al. Lancet, 2008

BIAS

POISE Trial



B-bloqueadores
33% Aumento en el Riesgo de Morir

Bernard et al. Lancet, 2008

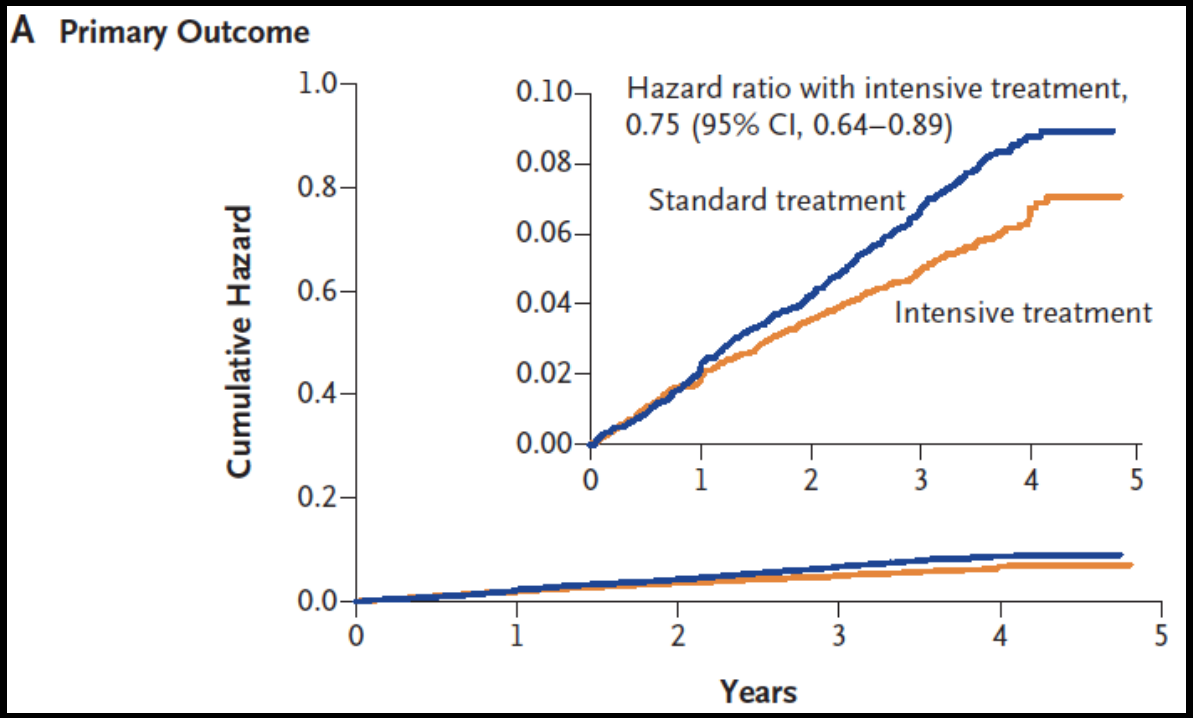
BIAS

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*



SPRINT SG, NEJM, 2015

BIAS

Table 2.

Outcome	Point Estimate RR 95% CI	I^2 or P value
Benefits		
All-Cause Mortality		
SPRINT	0.73 (0.60–0.90)	0.003
Xie et al.	0.91 (0.81-1.03)	NA
Trials <130 mmHg	0.91 (0.77-1.08)	29%
Trials <120 mmHg	0.87 (0.68-1.12)	60%
CV Mortality		
SPRINT	0.57 (0.38–0.85)	0.005
Xie et al.	0.91 (0.74-1.11)	NA
Trials <130 mmHg	0.80 (0.60-1.06)	25%
Trials <120 mmHg	0.76 (0.46-1.23)	59%
Stroke		
SPRINT	0.89 (0.63-1.25)	0.50
Xie et al.	0.78 (0.68-0.90)	12%
Trials <130 mmHg	0.80 (0.65-0.99)	28.2%
Trials <120 mmHg	0.82 (0.56-1.20)	55%

Outcome							NNT
Benefits							
Primary C							245
Myocardi							NS
Acute Cor							NS
Stroke							NS
Hearth Fa							345
Death fro							456
Death							83
Emergen serious a							**NNH**
Hypotens							76
Syncope							45
Bradycard							NS
Electrolyt							125
Injurious							NS
Acute Kidney Failure	324	2.6%	71% (36,112)*	-	-	-	56

Rodriguez-Gutierrez R, Montori VM, Guyatt GH, Evidence Based Medicine, 2016

BIAS

199 diabetes RCTs en Revistas Alto Impacto

Allocation concealment: 11%

Ciego: 42%

> 20% Loss to follow-up: 57%

Los mejores reportes* de métodos

Ensayos aleatorios financiados por corporaciones con fines de lucro

Montori VM et al, Diabetes Care 2008; 29: 1833-8

* Devereaux PJ et al. J Clin Epidemiol 2004; 57: 1232-6

BIAS

Sesgo (Bias) en RCTs

Aleatorización

Encubrimiento de la secuencia (Concelement)

Ciego*

FACIL

Pérdida de Pacientes (Follow-up)

Ensayo truncado por hallazgo beneficioso

Intention-to-treat Analysis

BIAS

SPIN

SPIN

High quality RCT

1715 HTN DM2 nephropathy

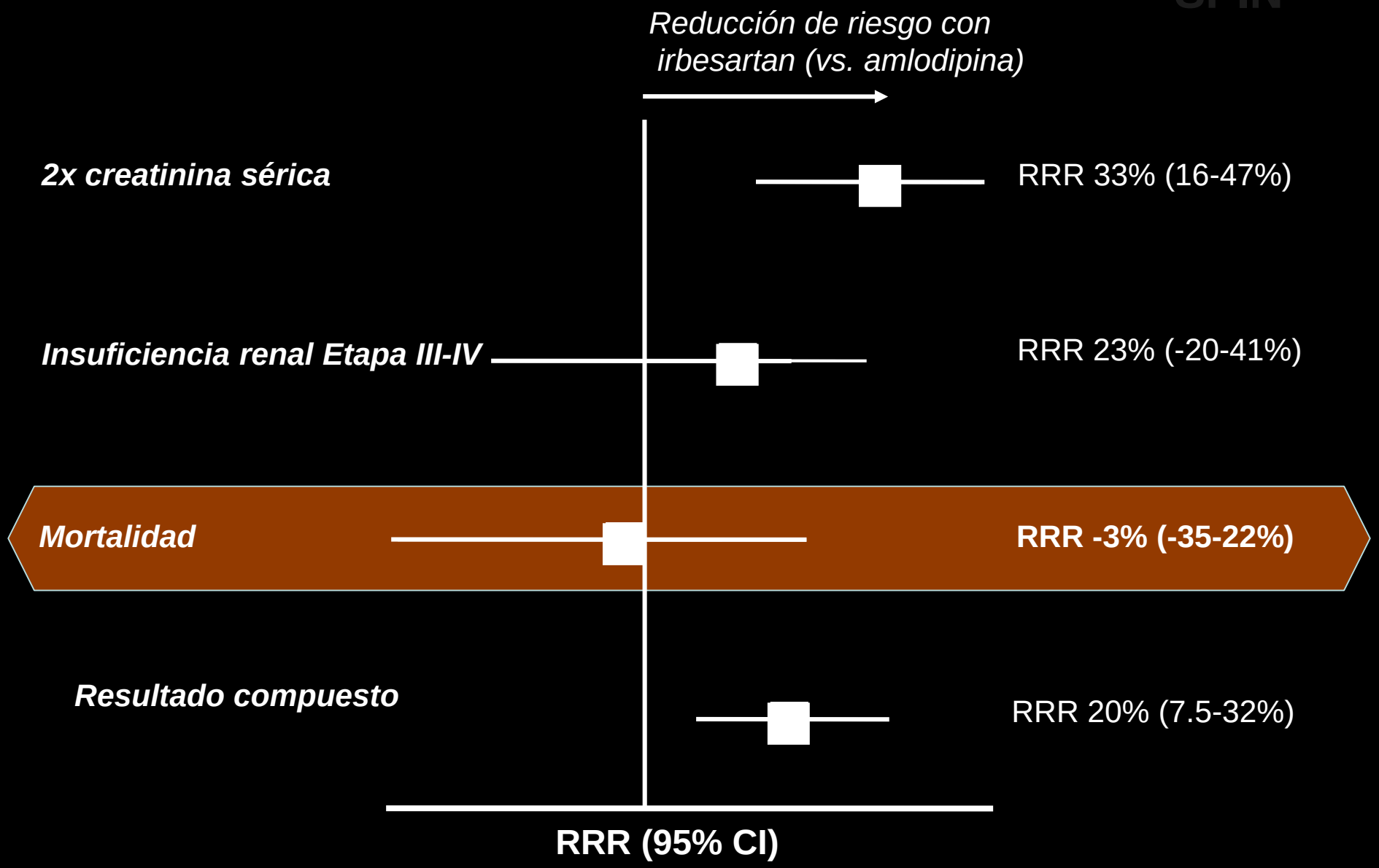
Amlodipine vs. ARA (Ibesartan)

2.6 years of follow-up

"El Tx con Irbesartan fue associado con una disminución del riesgo del objetivo primario* 23% menor que el grupo tomando amlodipino (P=0.006)"

*Creatinina al doble, enfermedad renal etapa III o IV, o muerte por cualquier causa.

Lewis EJ et al N Engl J Med 2005; 345: 851-60



Lewis EJ et al N Engl J Med 2005; 345: 851-60

DREAM Trial

‡Death from any cause (1.1% vs 1.3%) or diabetes (10.6% vs 25%).

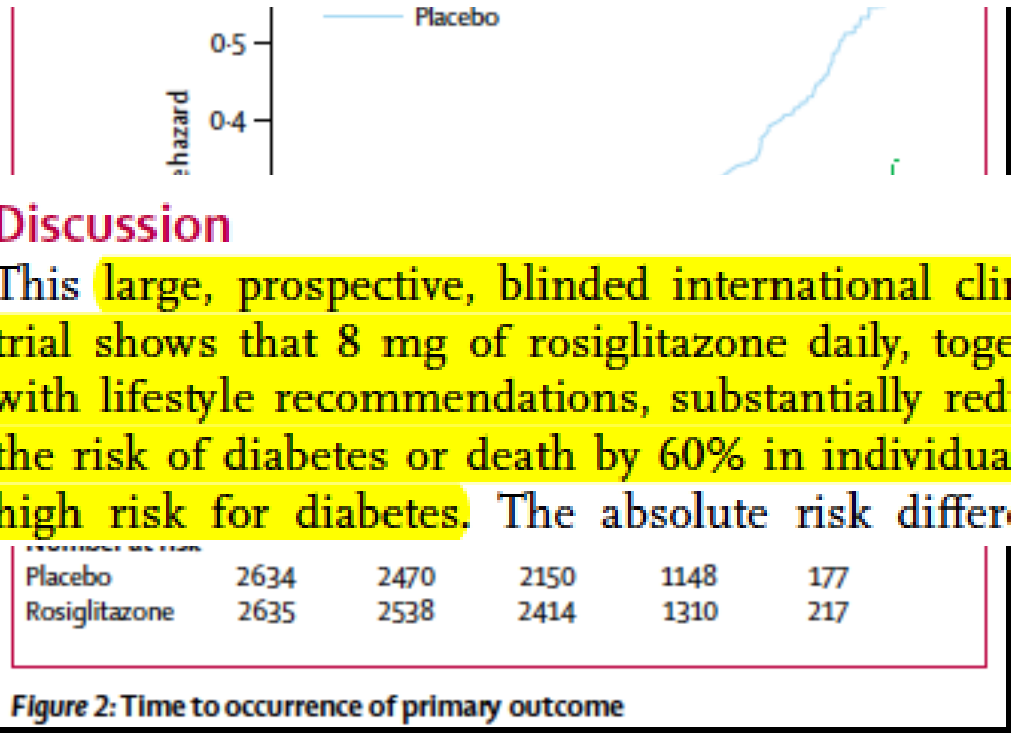


Figure 2: Time to occurrence of primary outcome

Discussion

This large, prospective, blinded international clinical trial shows that 8 mg of rosiglitazone daily, together with lifestyle recommendations, substantially reduces the risk of diabetes or death by 60% in individuals at high risk for diabetes. The absolute risk difference

Outcomes	Rosiglitazone	Placebo	RRR (95% CI)	NNT (CI)
Composite outcome‡	11.6%	26%	56% (50 to 62)	7 (7 to 8)

DREAM Invest. Lancet 2008

UKPDS 33: +4000 Pacientes DM2 x 10y

Cualquier Endpoint de Diabetes 12% RRR

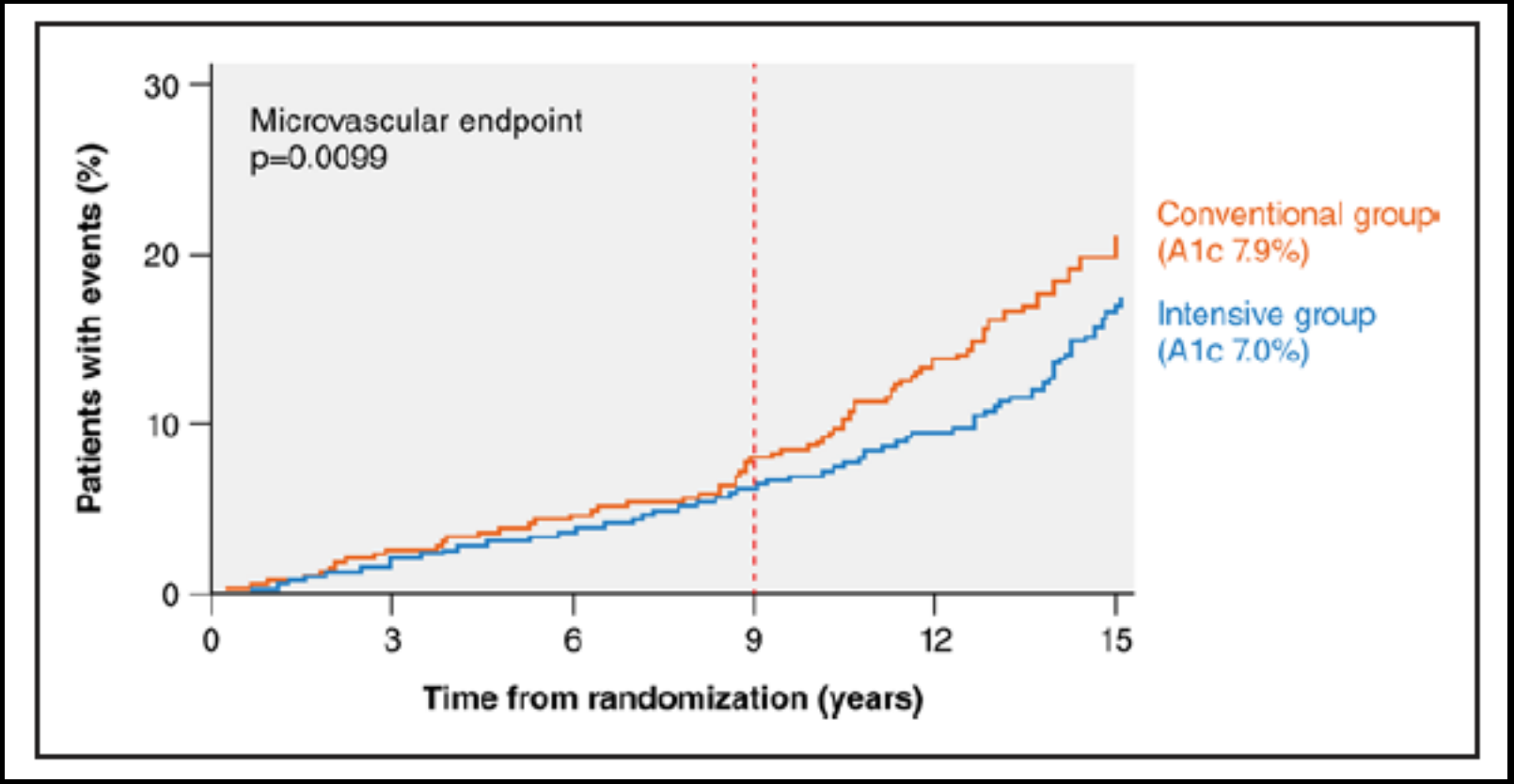
Muerte Repentina
Muerte por hipoglucemia
Muerte por hiperglucemia
IAM Fatal
IAM No-Fatal
Angina Inestable
ICC
Stroke
Enfermedad Renal Terminal
Amputación
Hemorragia Vitrea

Tx. Intensivo: 35.3%
Tx. Conservador: 38.5%
Diferencia: 3.2% (*P*=0.029)

Ceguera
Extracción de Catarata

Lancet 1998; 345: 800-11

¿De Inmediato?



Circulation. 2017;135:180–195.

¿Outcomes Intermedios o Surrogados?

Yudkin et al. BMJ 2009
Rodriguez-Gutierrez R. et al JAMA 2015

VIEWPOINT

Predicting the Overuse of PCSK-9 Inhibitors

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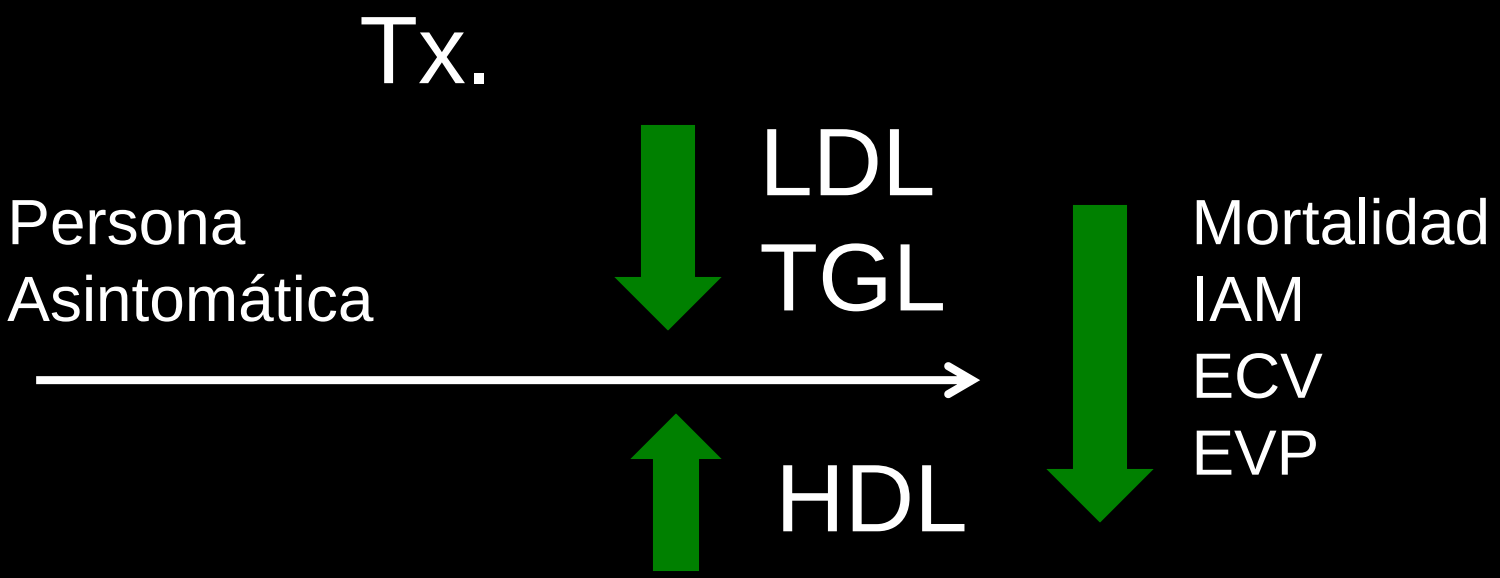
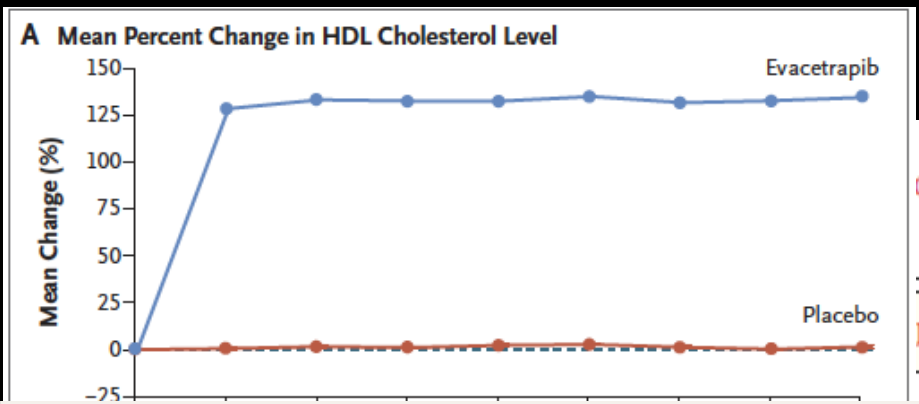
Knowledge and Evaluation Research Unit, Mayo Clinic, Rochester, Minnesota; and Division of Endocrinology, Diabetes, Metabolism, and Nutrition, Department of Medicine, Mayo Clinic, Rochester, Minnesota.



Rodriguez-Gutierrez R. et al JAMA 2015



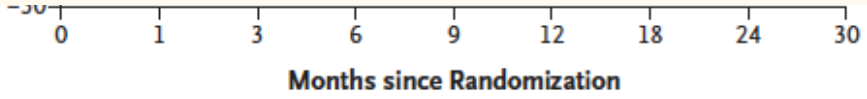
OURNAL of MEDICINE

L ARTICLE

Table 2. Primary and Secondary Efficacy End-Point Events and Lipid Effects.

Event or Laboratory Variable	Evacetrapib (N=6038)	Placebo (N=6054)	Hazard Ratio (95% CI)	P Value*
Primary composite end point — no. (%)†	779 (12.9)	776 (12.8)	1.01 (0.91 to 1.11)	0.91
Death from cardiovascular causes	143 (2.4)	166 (2.7)	0.86 (0.69 to 1.08)	0.19
Myocardial infarction	258 (4.3)	259 (4.3)	1.00 (0.84 to 1.18)	0.97
Stroke	94 (1.6)	98 (1.6)	0.96 (0.72 to 1.27)	0.77
Hospitalization for unstable angina	155 (2.6)	146 (2.4)	1.06 (0.85 to 1.33)	0.60
Coronary revascularization	487 (8.1)	485 (8.0)	1.01 (0.89 to 1.14)	0.94

and Steven E. Nissen, M.D., for t



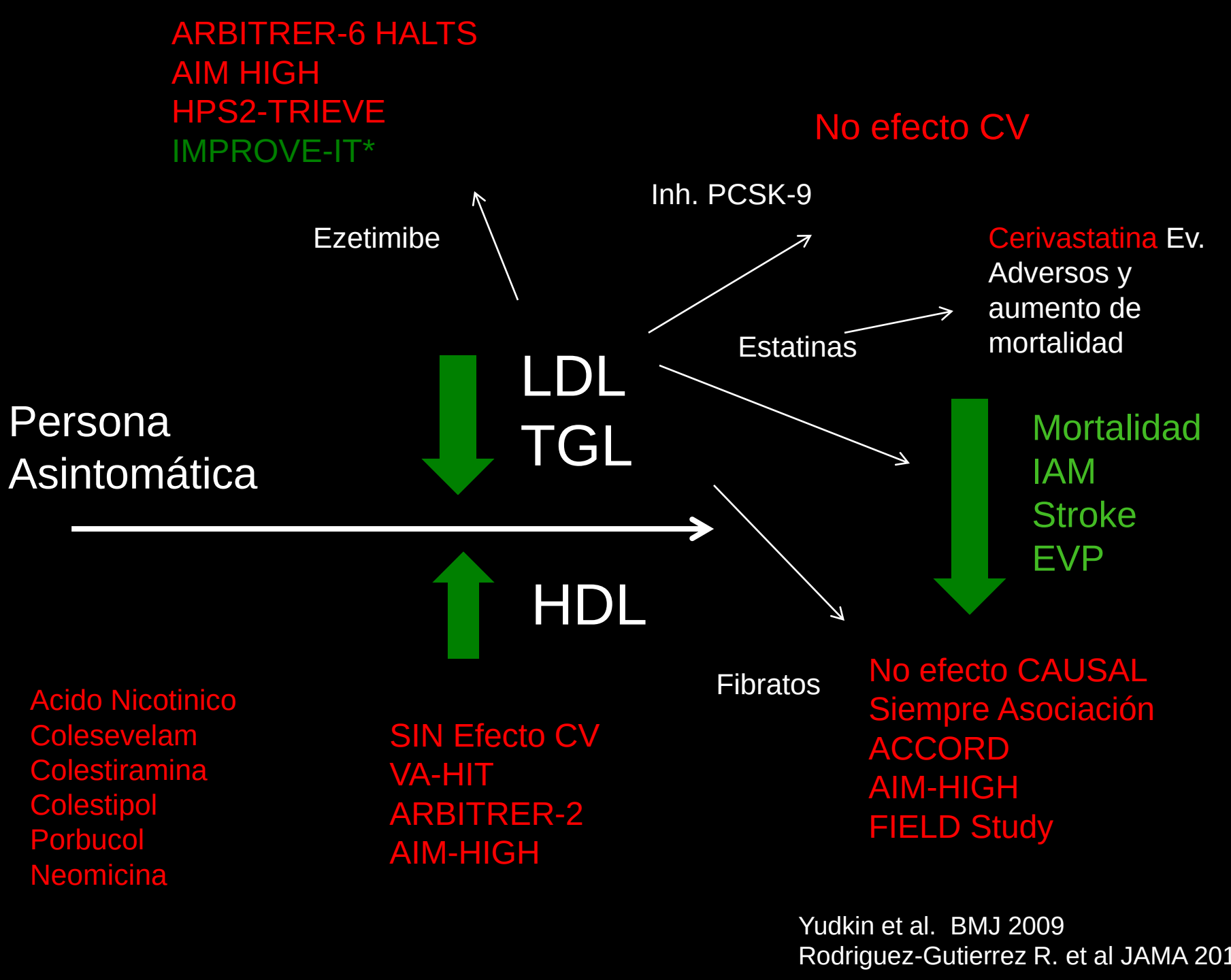
Mean Change at 3 Mo

Evacetrapib, −31.1±27.6%

Placebo, 6.0±29.0%

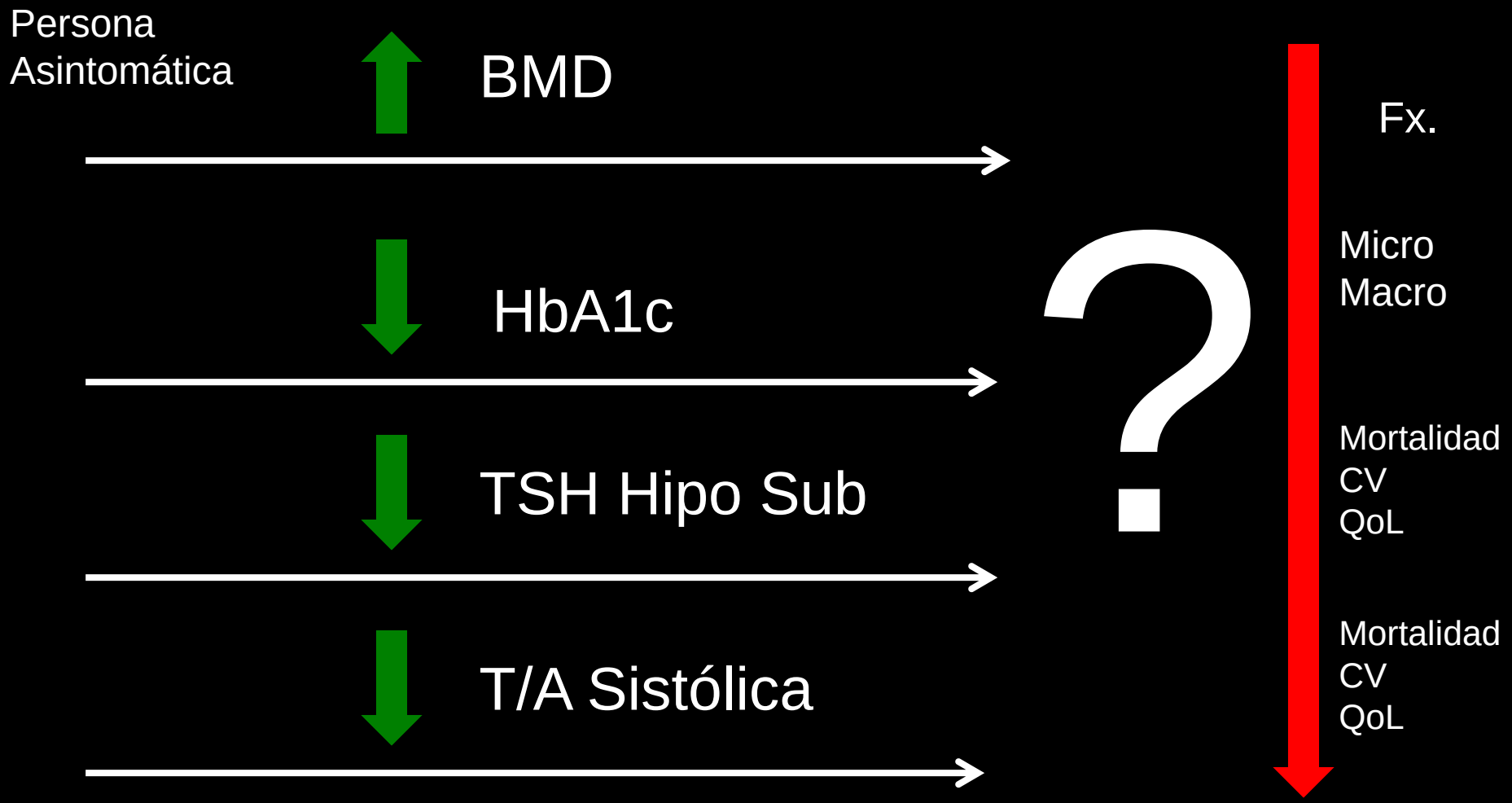
Difference, −37.1 percentage points (95% CI, −38.1 to −36.1); P<0.001

	Baseline	At 3 Mo
Evacetrapib	81.6±28.4 mg/dl	54.7±26.4 mg/dl
Placebo	81.1±27.8 mg/dl	83.7±30.8 mg/dl



Yudkin et al. BMJ 2009
Rodriguez-Gutierrez R. et al JAMA 2015

Medicina llena de Surrogates



Rodriguez-Gutierrez R. et al. Lancet Diab & Endo 2016

Outcomes (Desenlaces)

Outcomes crítcos, duros o de importancia al paciente (clinicamente importantes)

Endocntrados solamente en

1 de cada 5 RCTs en diabetes

Rodriguez-Gutierrez R. et al. Lancet Diab & Endo 2016
Ghandi G et al. JAMA 2008

SPIN

Comparaciones inadecuadas

Resultados compuestos mal construidos

Resultados de bajo valor clínico

Cambio de la definicion de los resultados post hoc

Analisis de subgrupos en abundancia e inadecuados

Discusión y conclusiones

Alto riesgo: Efectos de tratamiento grandes*

BIAS

SPIN

REPORTE SESGADO

Sesgo de Reporte

102 protocolos daneses | 122 reportes publicados (2003)

50% de resultados reportados incompletos

La Posibilidad de que se reporte un resultado completamente es

2:1

Si el resultado es Positivo

JAMA. 2010;291:2457-2465.

Sesgo de Publicación

+ 4x -

PUBLICADOS:

41% de ensayos con resultados negativos

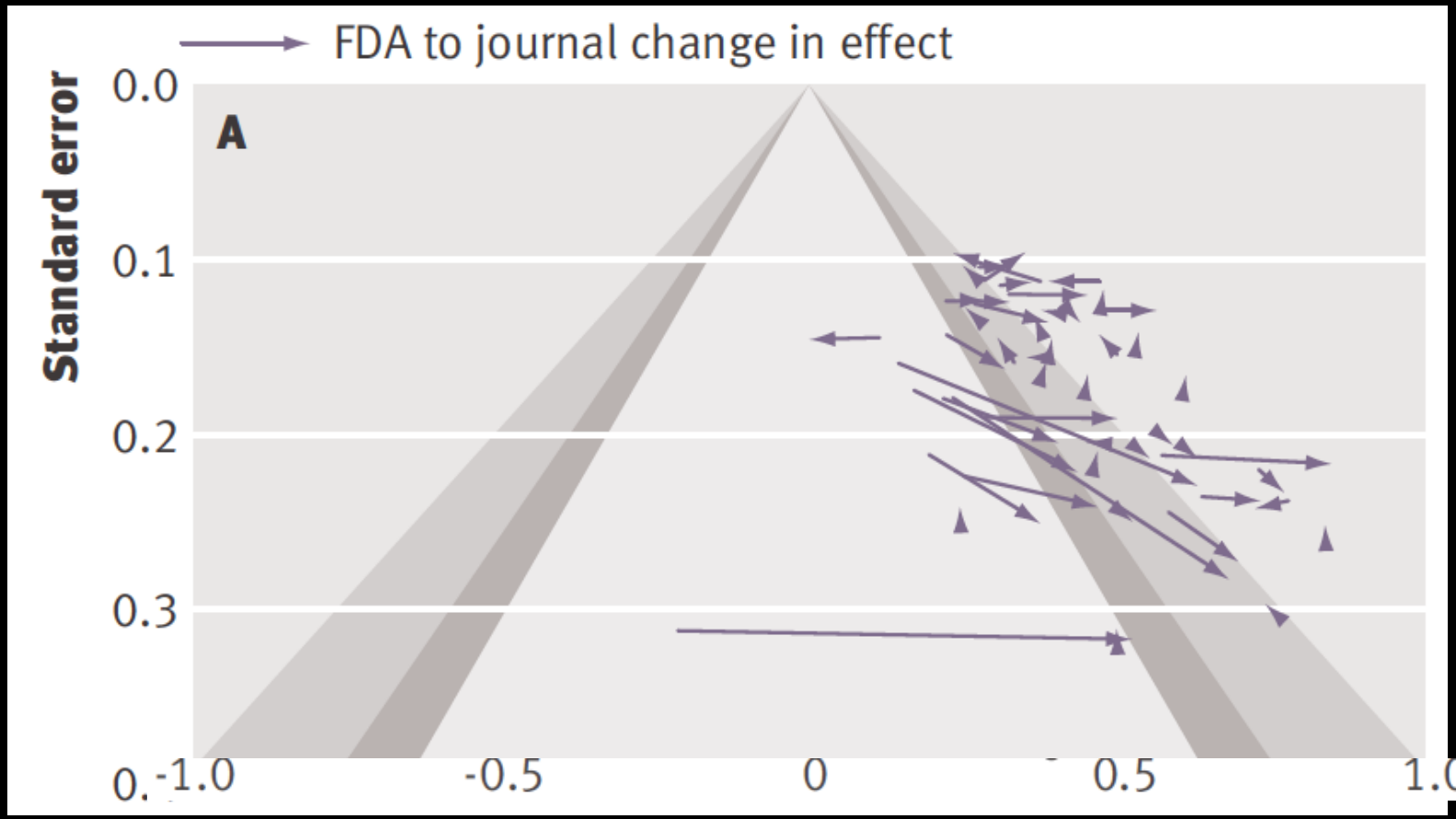
73% de los ensayos positivos

Ensayos positivos se publican más rápido

Hopewell S et al. Cochrane Review 2013

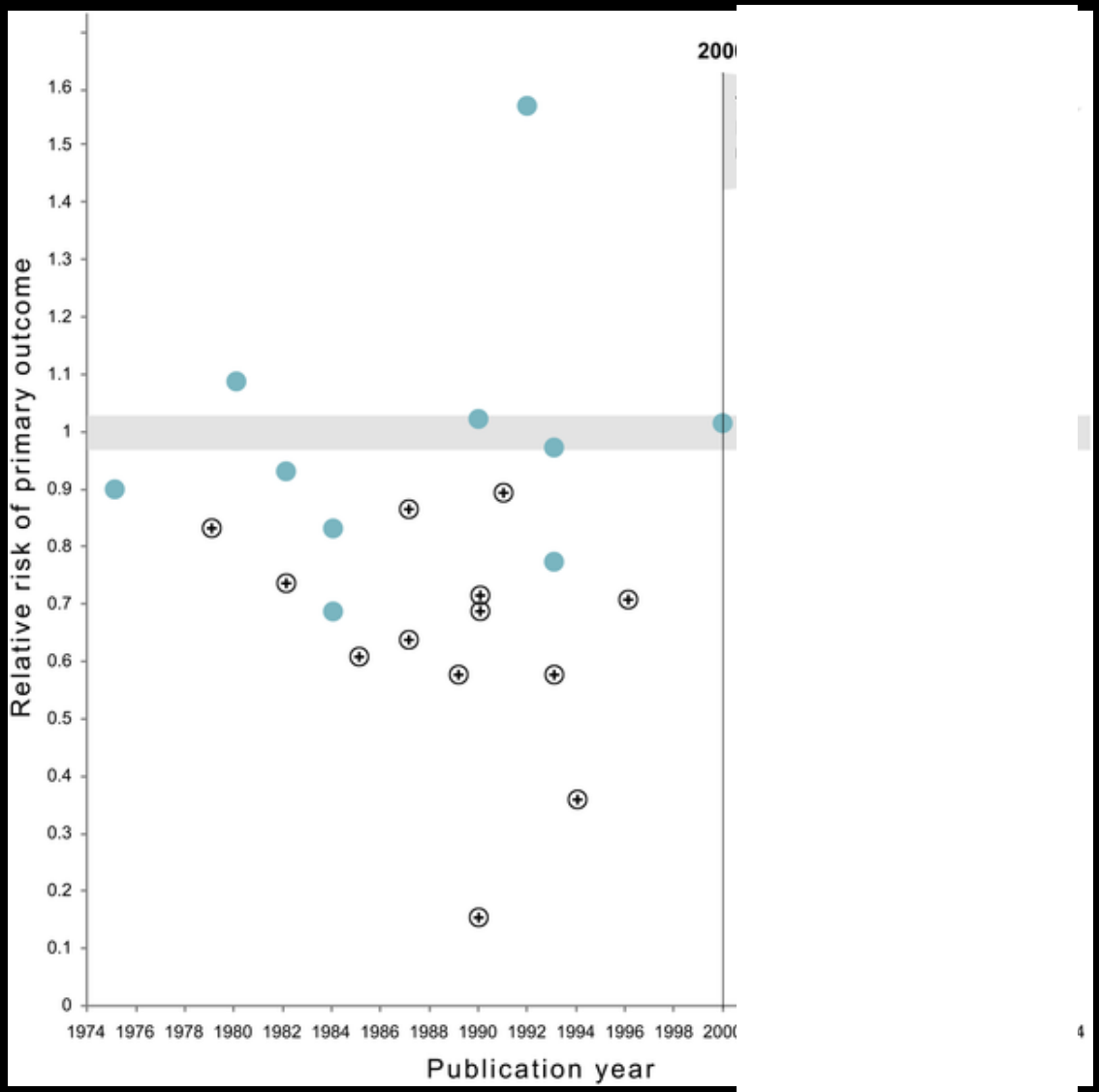
Sesgo de Reporte

Antidepresivos FDA vs. Artículos Publicados



Moreno et al. BMJ 2009

Transparencia y Efecto de Tratamiento



50 large NHLBI trials on pharmaceutical and dietary supplement interventions.

Kaplan RM, Irvin VL (2015) PLoS ONE 2015 10(8)

BIAS

SPIN

BIASED REPORTING

FRAUD?

Evidence-based guidelines

2013 AACE Diabetes Guidelines

*16 de 19 miembros conflicto de Interes entre todos superior a los $3.0 Millones de Dolares

Gionfrido M. et al. JAMA Int Med 2013

GLYCEMIC CONTROL ALGORITHM

LIFESTYLE THERAPY
(Including Medically Assisted Weight Loss)

Entry A1C < 7.5%

MONOTHERAPY*

- ✓ Metformin
- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Dual Therapy

Entry A1C ≥ 7.5%

DUAL THERAPY*

MET or other 1st-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ✓ DPP-4i
- ⚠ TZD
- ⚠ Basal Insulin
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to Triple Therapy

TRIPLE THERAPY*

MET or other 1st-line agent + 2nd-line agent +

- ✓ GLP-1 RA
- ✓ SGLT-2i
- ⚠ TZD
- ⚠ Basal insulin
- ✓ DPP-4i
- ✓ Colesevelam
- ✓ Bromocriptine QR
- ✓ AGi
- ⚠ SU/GLN

If not at goal in 3 months proceed to or intensify insulin therapy

Entry A1C > 9.0%

SYMPTOMS

NO	YES
DUAL Therapy OR TRIPLE Therapy	INSULIN ± Other Agents

ADD OR INTENSIFY INSULIN

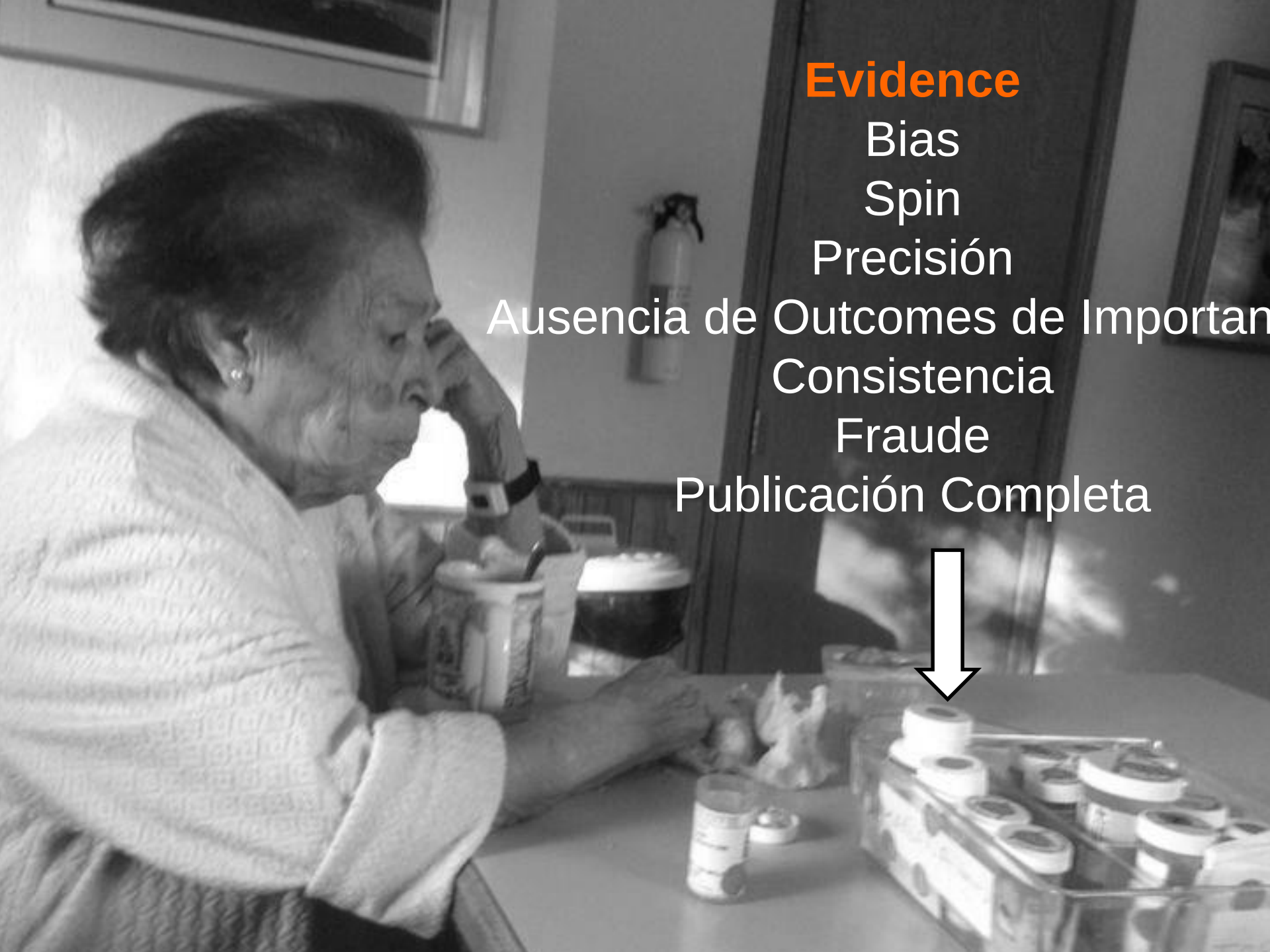
Refer to Insulin Algorithm

LEGEND

- ✓ Few adverse events and/or possible benefits
- ⚠ Use with caution

* Order of medications represents a suggested hierarchy of usage; length of line reflects strength of recommendation

PROGRESSION OF DISEASE


Evidence
Bias
Spin
Precisión
Ausencia de Outcomes de Importan
Consistencia
Fraude
Publicación Completa

¿Qué hacer con esto?

Segundo Principio de MBE

La evidencia por si misma NUNCA será suficiente para la toma de decisiones.

Valores Preferencias

Shared Decision Making

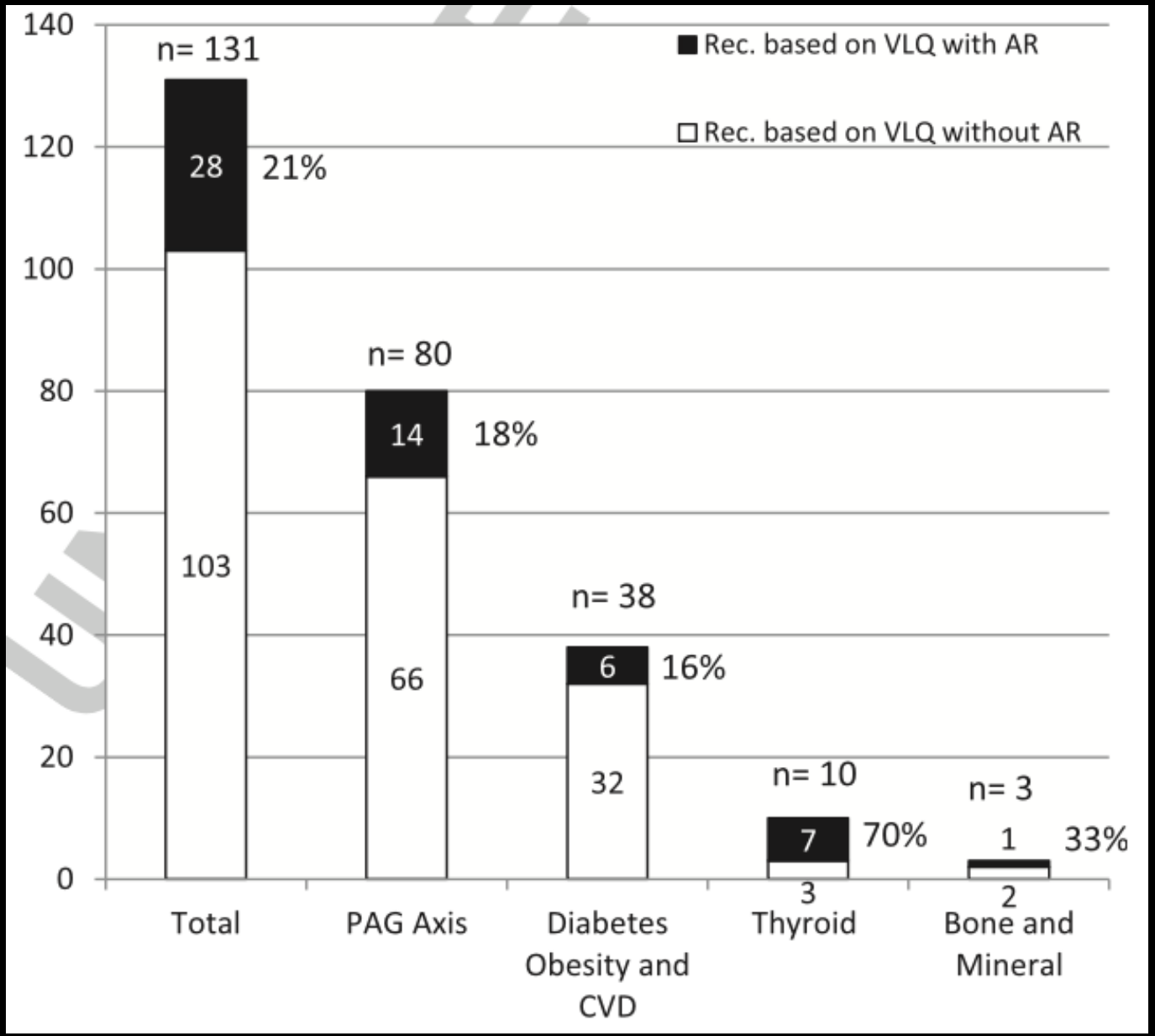
1. Ausencia de Alto Nivel de Evidencia

RESEARCH ARTICLE Open Access

Is the endocrine research pipeline broken? A systematic evaluation of the Endocrine Society clinical practice guidelines and trial registration

Rene Rodriguez-Gutierrez[1†] Naykky Singh Ospina[1†], Juan P. Brito[1], William F. Young Jr.[2] and Victor M. Montori[1*]

Rodriguez-Gutierrez R. et al. BMC Medicine, 2015



Rodriguez-Gutierrez R. et al. BMC Medicine 2015

Solidez de la Evidencia…
¿Solo Endocrinología?

Recomendaciones:	Clase Ia	Clase IIb-IIIc
• Cardiología	11%	48%
• Infectología	14%	55%

JACC Vol. 63, No. 25, 2014

Clinical Infectious Diseases 2010;50:133–64

2. Aun en Presencia de Alto Nivel de Evidencia

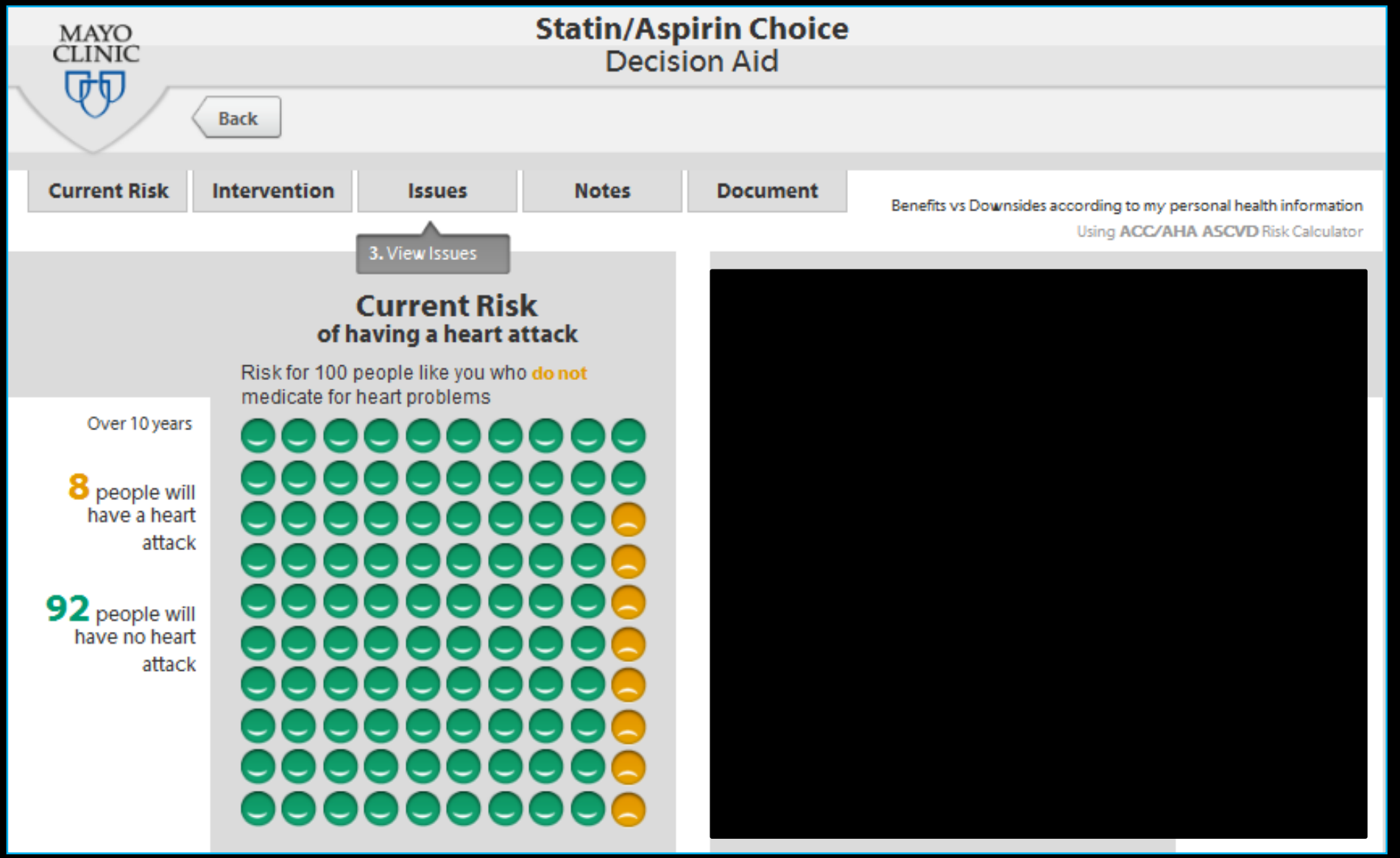
¿Cómo comunicar o compartir la evidencia?

Px. Femenina de 63 años de edad

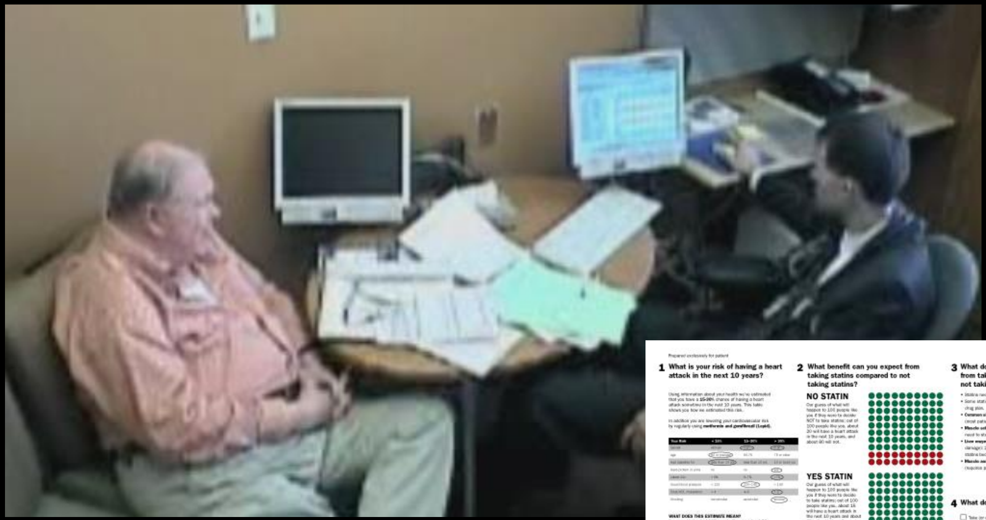
DM +, HTA JNC8 Etapa 1

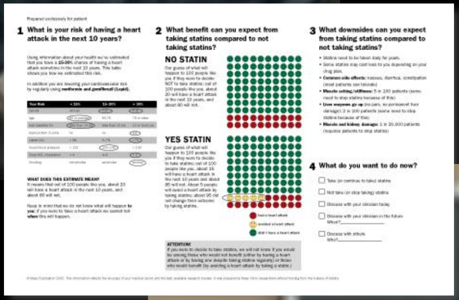
Col Total 200 Col LDL 140

Con Riesgo CV ACC/AHA 10-años 8%



Rodriguez-Gutierrez R. et al. Lancet Diab & Endo 2016





Prepared exclusively for patient

1 What is your risk of having a heart attack in the next 10 years?

WHAT DOES THIS ESTIMATE MEAN?

2 What benefit can you expect from taking statins compared to not taking statins?

NO STATIN

YES STATIN

ATTENTION!
If you were to decide to take statins, we will not know if you would be among those who would not benefit (either by having a heart attack or by having one despite taking statins regularly) or those who would benefit (by avoiding a heart attack by taking a statin.)

3 What downsides can you expect from taking statins compared to not taking statins?

- Statins need to be taken daily for years.
- Some statins may cost less to you depending on your drug plan.
- **Common side effects:** nausea, diarrhea, constipation (most patients can tolerate)
- **Muscle aching/stiffness:** 5 in 100 patients (some need to stop statins because of this)
- **Liver enzymes go up** (no pain, no permanent liver damage): 2 in 100 patients (some need to stop statins because of this)
- **Muscle and kidney damage:** 1 in 10,000 patients (requires patients to stop statins)

4 What do you want to do now?

- ☐ Take (or continue to take) statins
- ☐ Not take (or stop taking) statins
- ☐ Discuss with your clinician today
- ☐ Discuss with your clinician in the future When?________
- ☐ Discuss with others Who?________

Cual es es aspecto de su tratamiento de diabetes que le gustaria discutir a continuación?

Mullan et al JAMA Int Med 2009

The body of evidence

Cochrane Systematic review of 115 RCTs

Compared to usual care, decision aids:

Increase patient involvement by 34% (+++-)

Increase patient knowledge of options by 13% (++++)

Increase consultation time by ~2.6 minutes

Reduce decisional conflict by ~7%

Reduce % undecided by 40%

Increase in Adherence 25-50%

No consistent,
health outcomes or costs

Segundo Principio de MBE

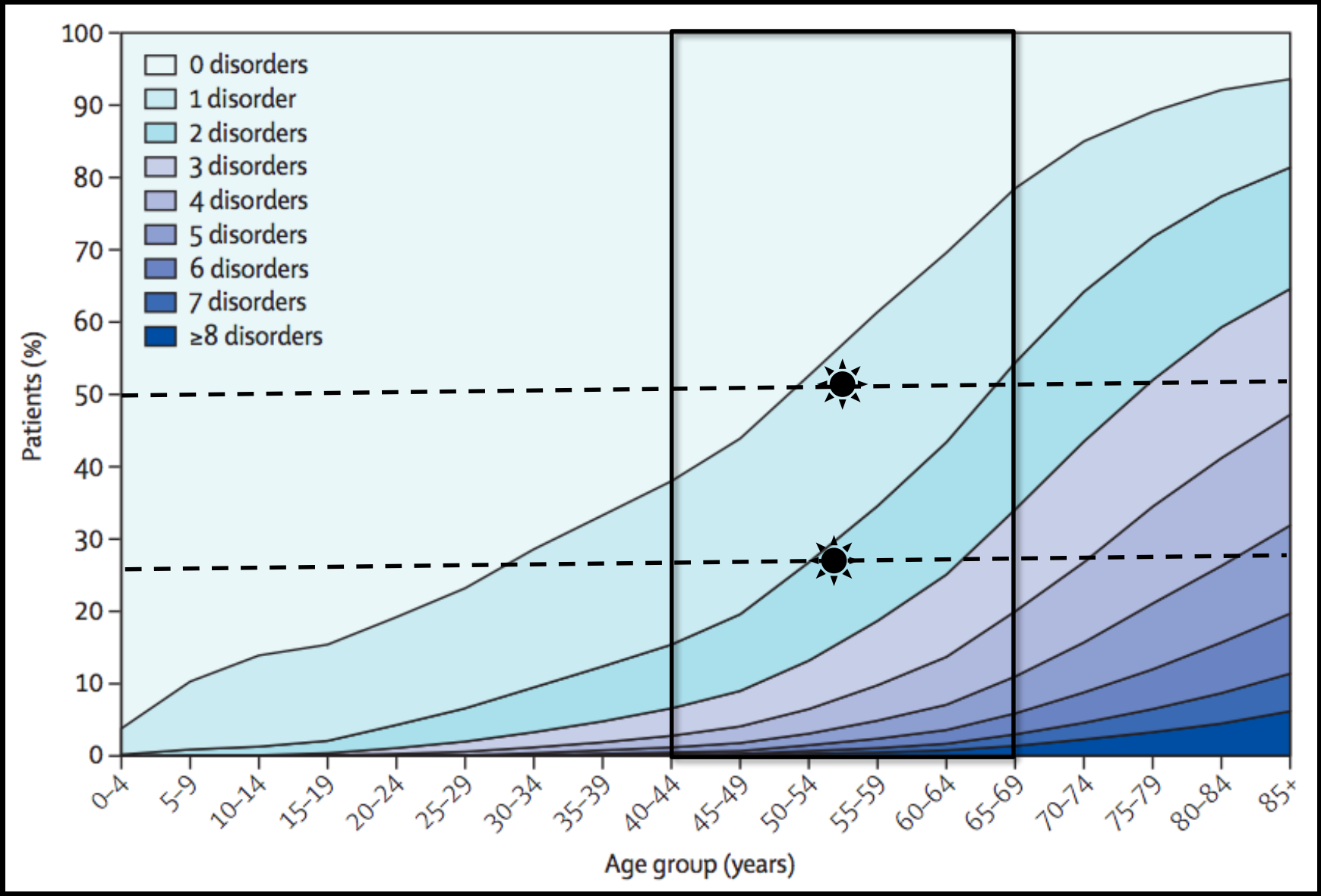
La evidencia por si misma NUNCA será suficiente para la toma de decisiones.

Valores Preferencias

Contexto

Shared Decision Making

Minimally Disruptive Medicine



Barnett et al. Lancet 2012

Rene Rodriguez-Gutierrez, MD
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Kasia J. Lipska, MD
Section of Endocrinology, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut.

Rozalina G. McCoy, MD, MSc
Division of Primary Care Internal Medicine, Department of Medicine, Mayo Clinic, Rochester, Minnesota; and Department of Health Sciences Research, Mayo Clinic, Rochester, Minnesota.

TEACHABLE MOMENT

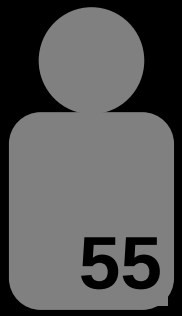
LESS IS MORE

Intensive Glycemic Control in Type 2 Diabetes Mellitus—A Balancing Act of Latent Benefit and Avoidable Harm
A Teachable Moment

Sra. Maria

Metformina

Sitagliptina



Diabetes

Insulina

Rodriguez-Gutierrez R. et al. JAMA Internal Medicine 2016

Sra.Maria

3 2 1

Transportarse a Consultas

Nutrióloga

Salida del trabajo

Los números no cuadran

108

Endocrinólogo

Todo para ayer

Obeso

Colesterol alto

LDL alto

Llevar trabajo a casa

Evitar la sal, las grasas, los carbohidratos

hipoteca

Trabajar!

Metformina

A1c 8.5%

deuda

Insulina

Diabetes

seguro

Hipertensión

Hipoglucemias

Problemas OH

Depresión

Beta-bloqueador

HCTZ

Insomnio

Hija **regresó** a casa

Ejercicio

2 bellas niñas

Dolor

Neuropatía

Lumbalgia

Revisar los pies

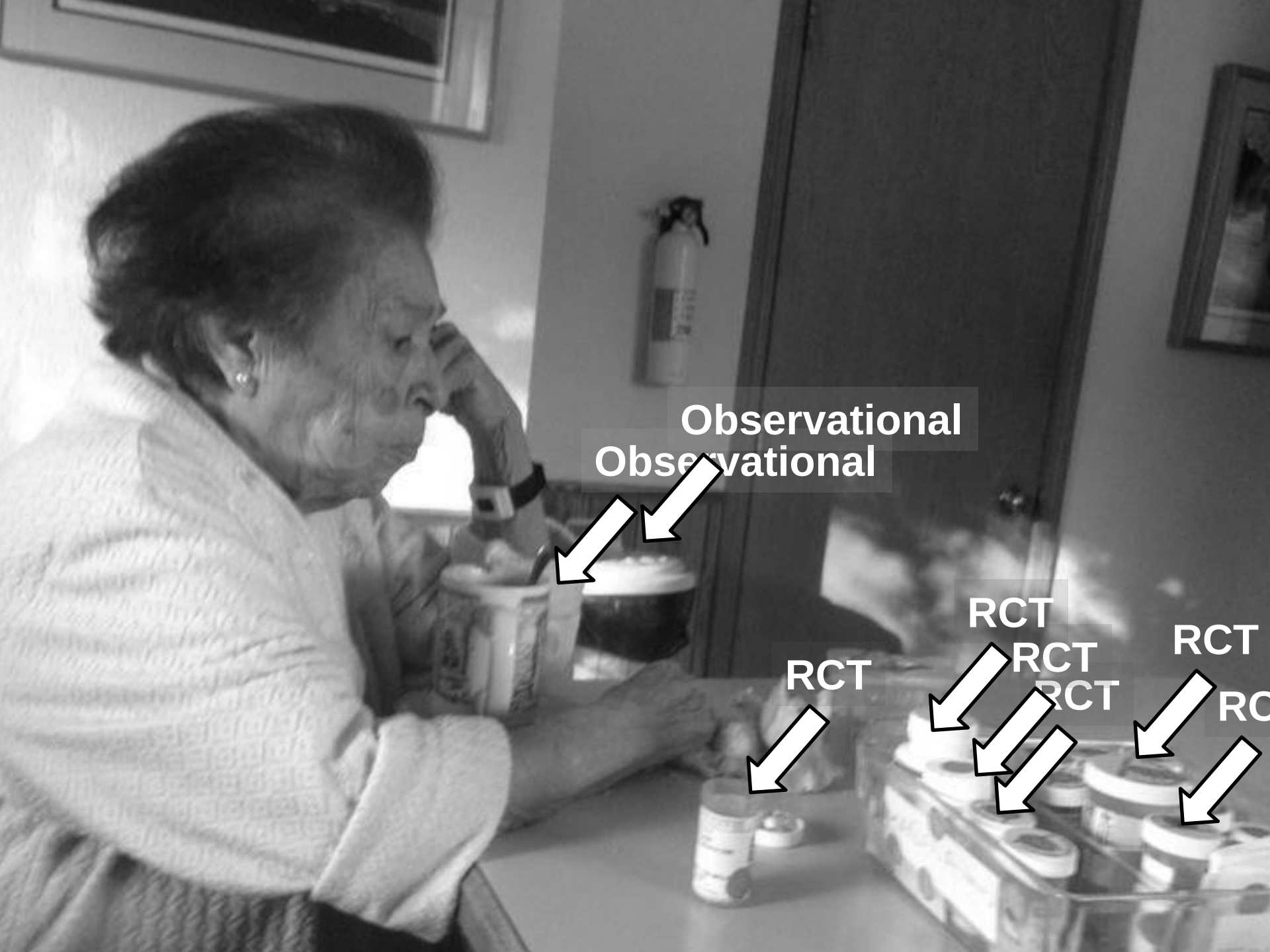
Podólogo

Monitorizar azúcar

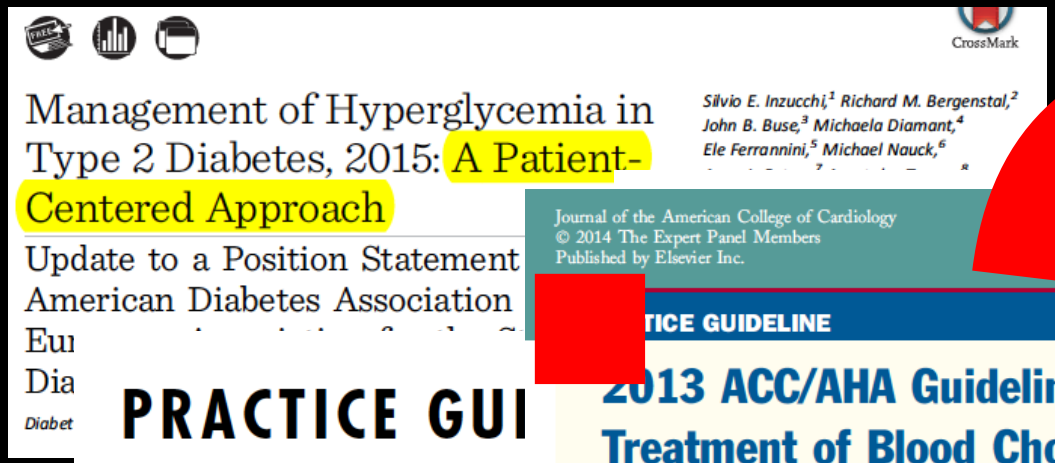
Oftalmólogo

Tomar las tabletas

Rodriguez-Gutierrez R. et al. JAMA Internal Medicine 2016


Observational
Observational
RCT
RCT
RCT
RCT
RCT
RCT
RC


¿Px. con Mal Apego a Tx?



Management of Hyperglycemia in Type 2 Diabetes, 2015: A Patient-Centered Approach

Update to a Position Statement

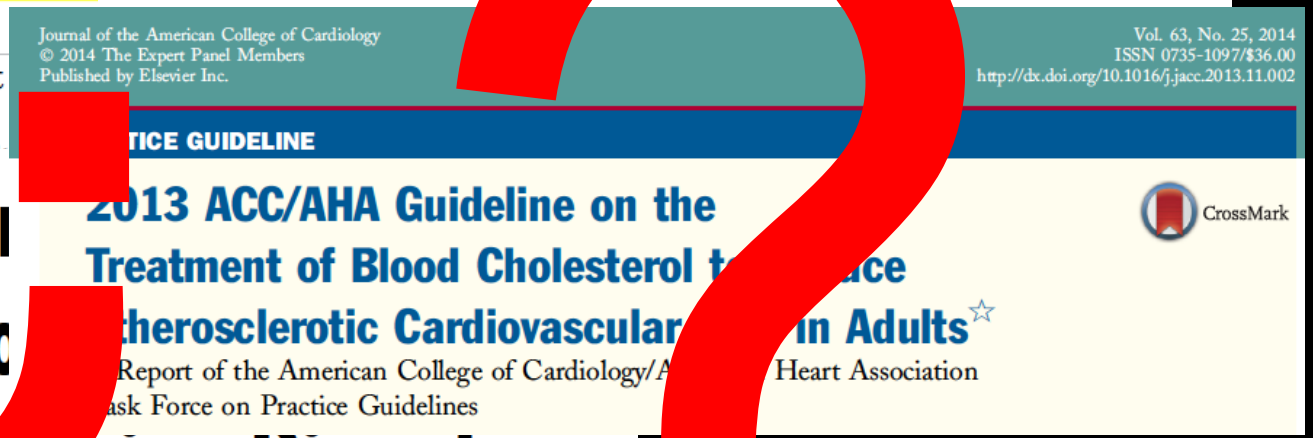
American Diabetes Association

Eu

Dia

Diabet

Silvio E. Inzucchi,[1] Richard M. Bergenstal,[2] John B. Buse,[3] Michaela Diamant,[4] Ele Ferrannini,[5] Michael Nauck,[6]



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http://dx.doi.org/10.1016/j.jacc.2013.11.002

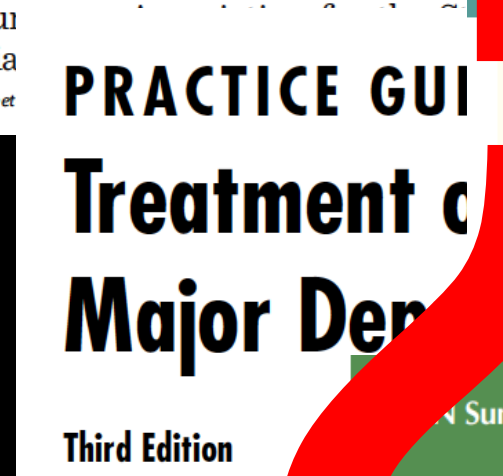
TICE GUIDELINE

2013 ACC/AHA Guideline on the Treatment of Blood Cholesterol t ace therosclerotic Cardiovascular in Adults☆

Report of the American College of Cardiology/A Heart Association

ask Force on Practice Guidelines

CrossMark

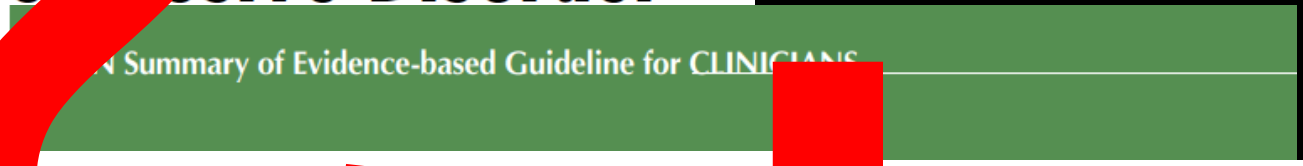


PRACTICE GUI

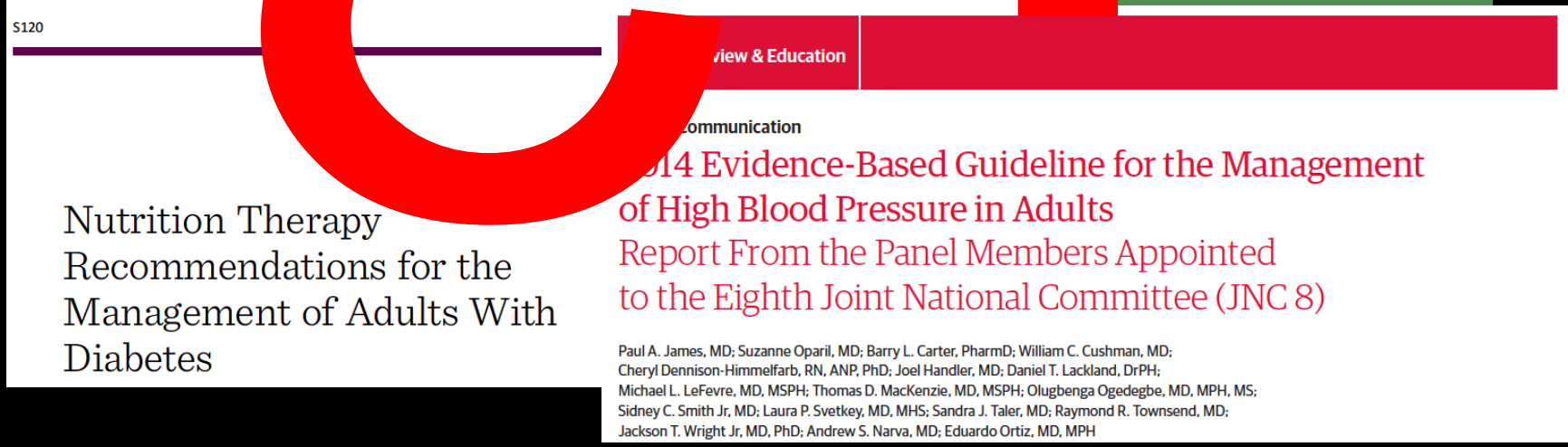
Treatment c

Major Dep ssive Disorder

Third Edition



N Summary of Evidence-based Guideline for CLINICIANS



S120

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ommunication

Nutrition Therapy Recommendations for the Management of Adults With Diabetes

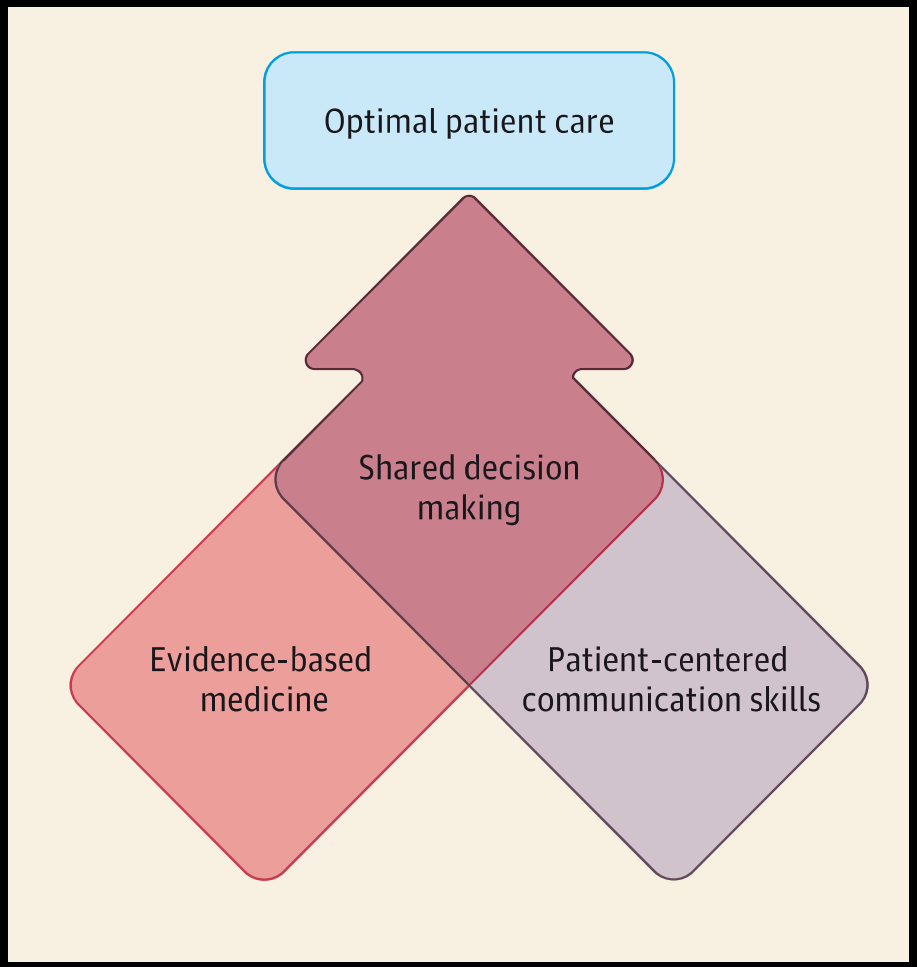
014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults

Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8)

Paul A. James, MD; Suzanne Oparil, MD; Barry L. Carter, PharmD; William C. Cushman, MD; Cheryl Dennison-Himmelfarb, RN, ANP, PhD; Joel Handler, MD; Daniel T. Lackland, DrPH; Michael L. LeFevre, MD, MSPH; Thomas D. MacKenzie, MD, MSPH; Olugbenga Ogedegbe, MD, MPH, MS; Sidney C. Smith Jr, MD; Laura P. Svetkey, MD, MHS; Sandra J. Taler, MD; Raymond R. Townsend, MD; Jackson T. Wright Jr, MD, PhD; Andrew S. Narva, MD; Eduardo Ortiz, MD, MPH

Entonces porque Molestarnos con EBM?

Aun así tenemos que tomar decisiones…

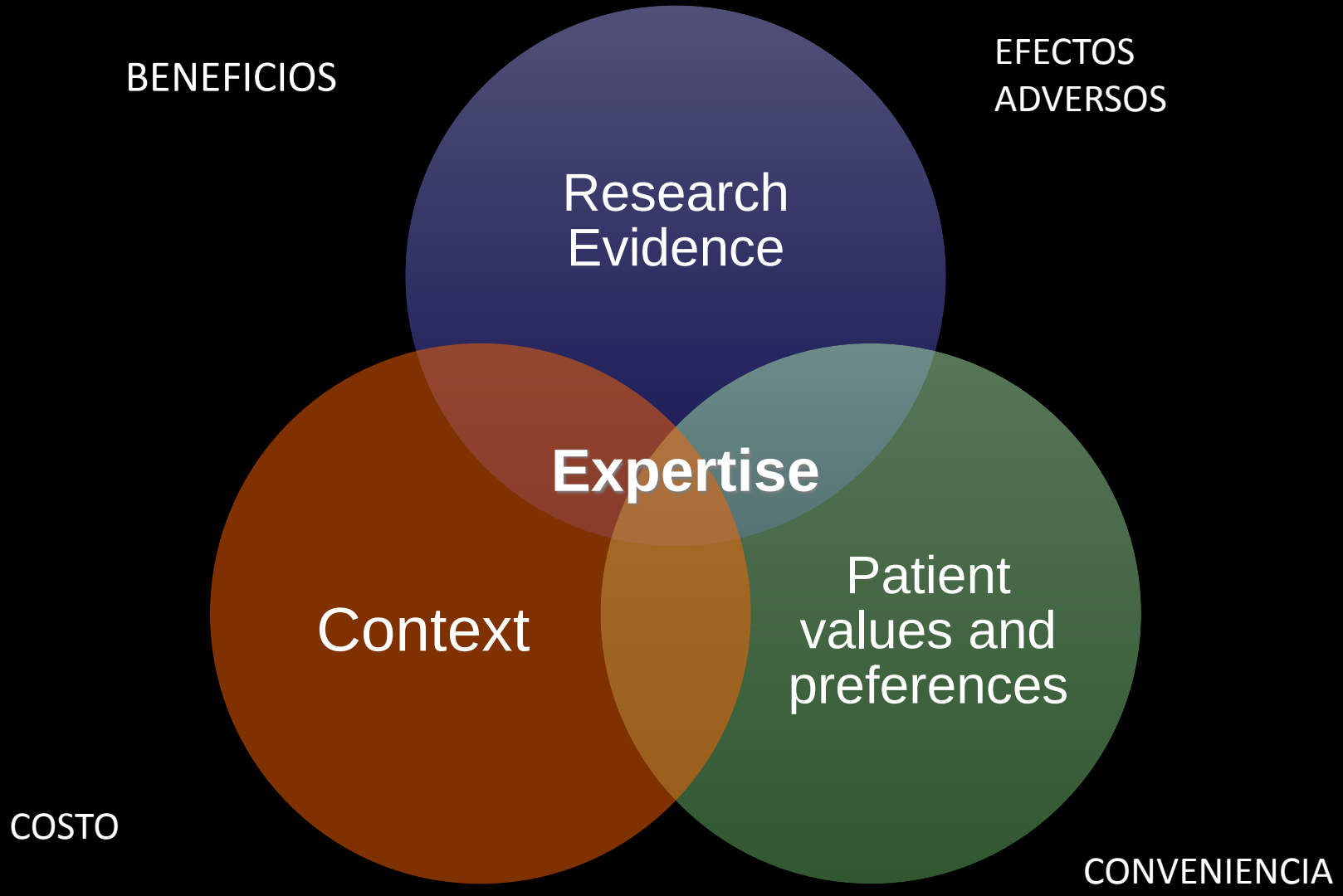


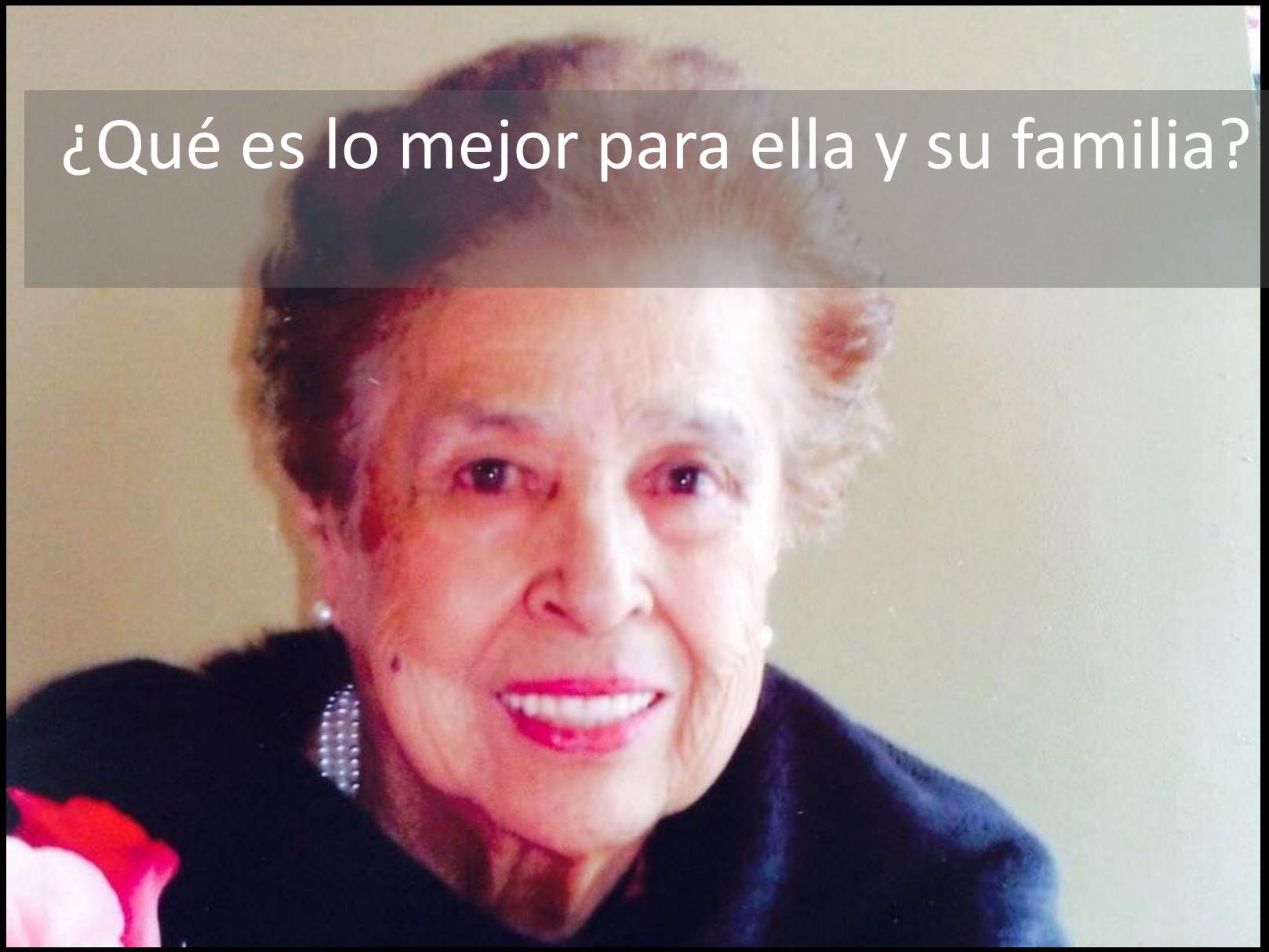
Sin SDM, MBE es una tirania, y no se puede traducir en cuidado del paciente optimo pues se pierde el contexto.

Sin MBE, SDM no es posible pues las preferencias NO serían basadas sobre la realidad.

Hoffmann TC et al JAMA 2014

MBE-TOMA DE DECISIONES




¿Qué es lo mejor para ella y su familia?

Gracias

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rodriguezgutierrez.rene@mayo.edu