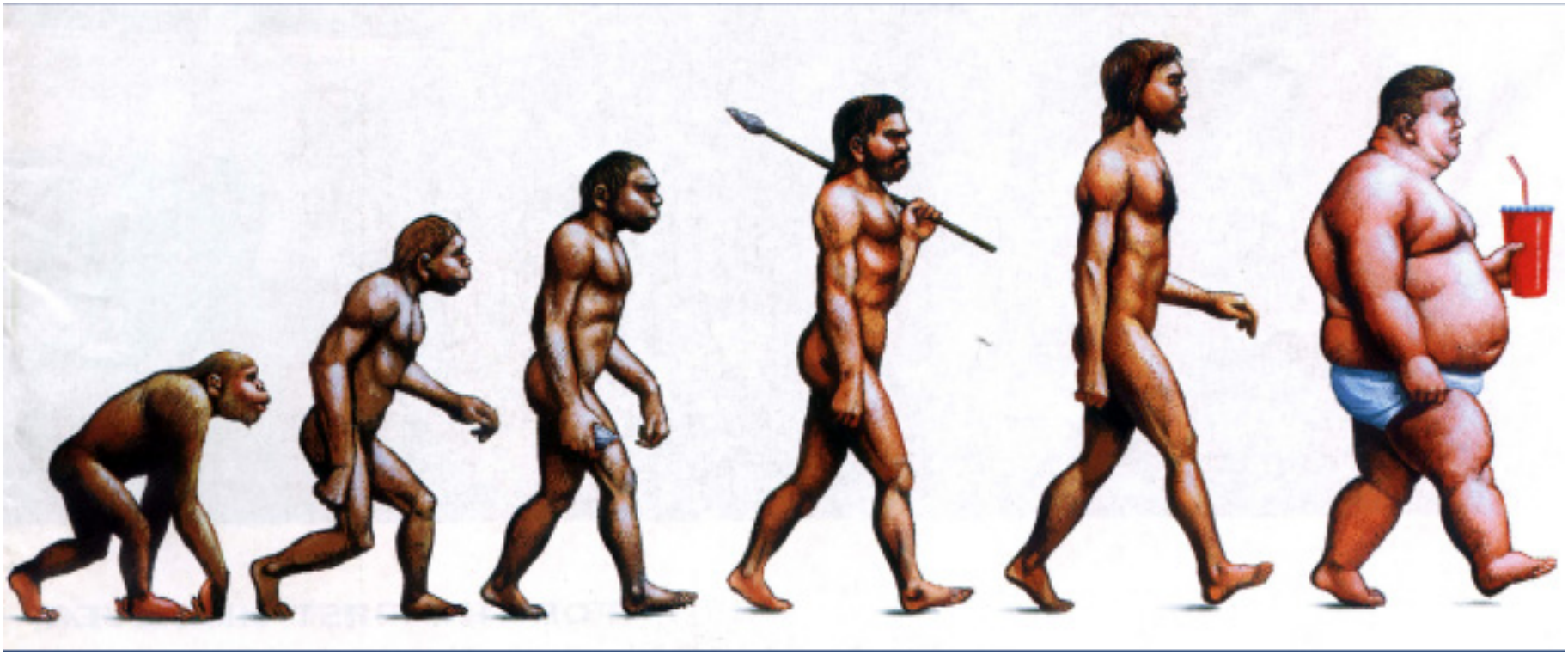
Diabète

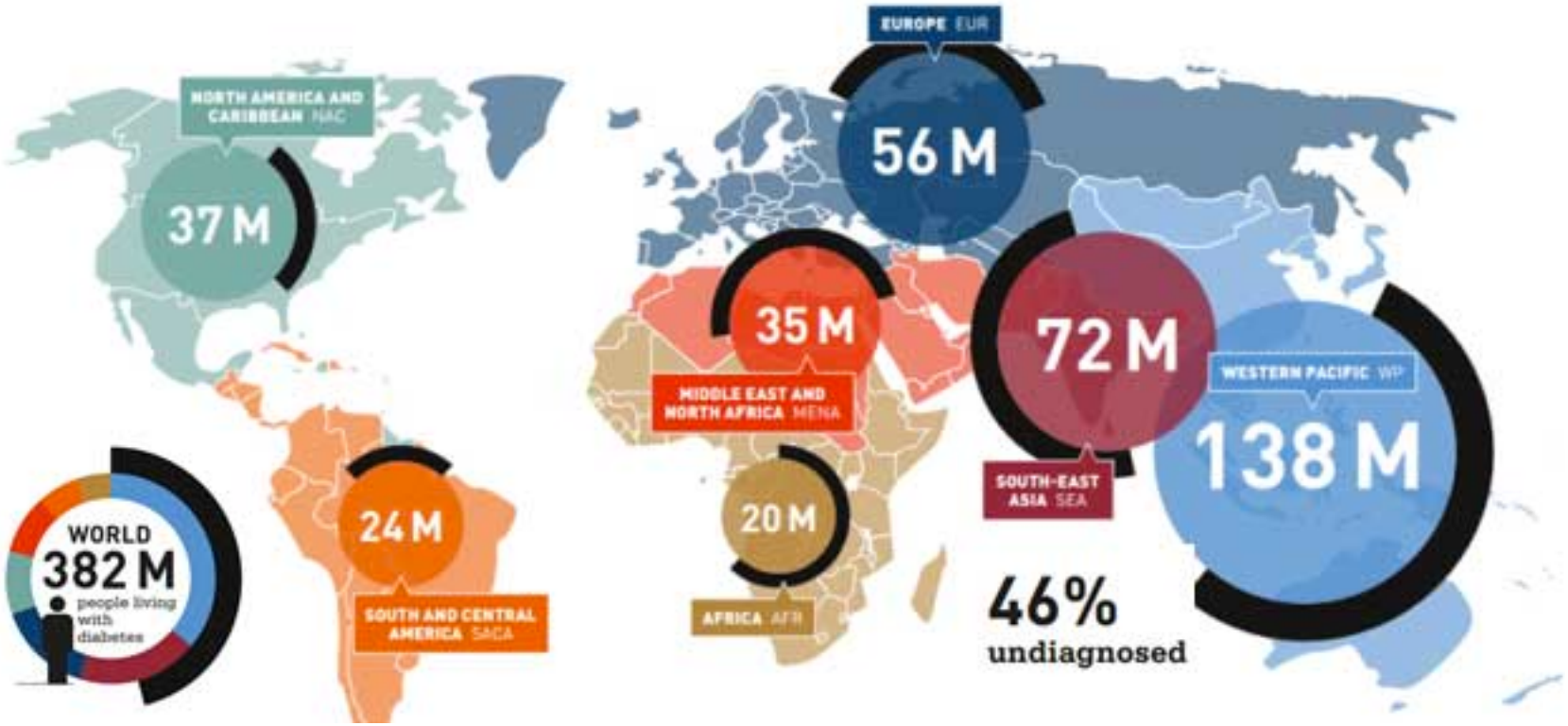
Patrick HENRY
Cardiology – Lariboisiere Hospital – AP-HP
University Denis Diderot Paris VII
Paris - France

Conflits d’intérêt

- Amgen
- Astra-Zeneca
- Bayer
- Daichi
- Lilly
- MSD
- Novo



IF DIABETES WERE **A COUNTRY,** IT WOULD BE THE

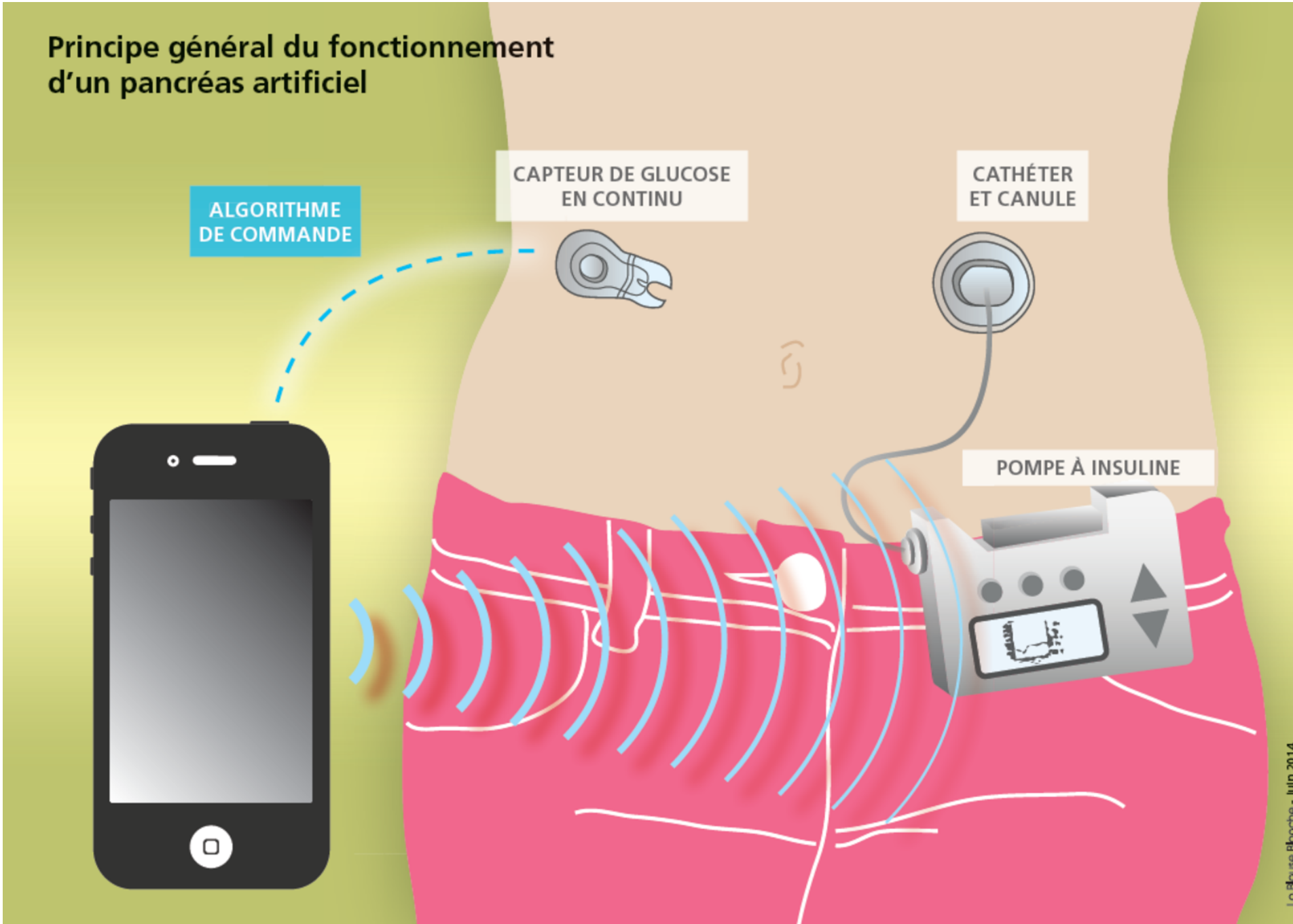

EUROPE EUR
56 M
NORTH AMERICA AND CARIBBEAN NAC
37 M
35 M
MIDDLE EAST AND NORTH AFRICA MENA
72 M
WESTERN PACIFIC WP
138 M
SOUTH-EAST ASIA SEA
20 M
AFRICA AFR
24 M
SOUTH AND CENTRAL AMERICA SACA
WORLD
382 M
people living with diabetes
46%
undiagnosed

Les patients traités pour le diabète

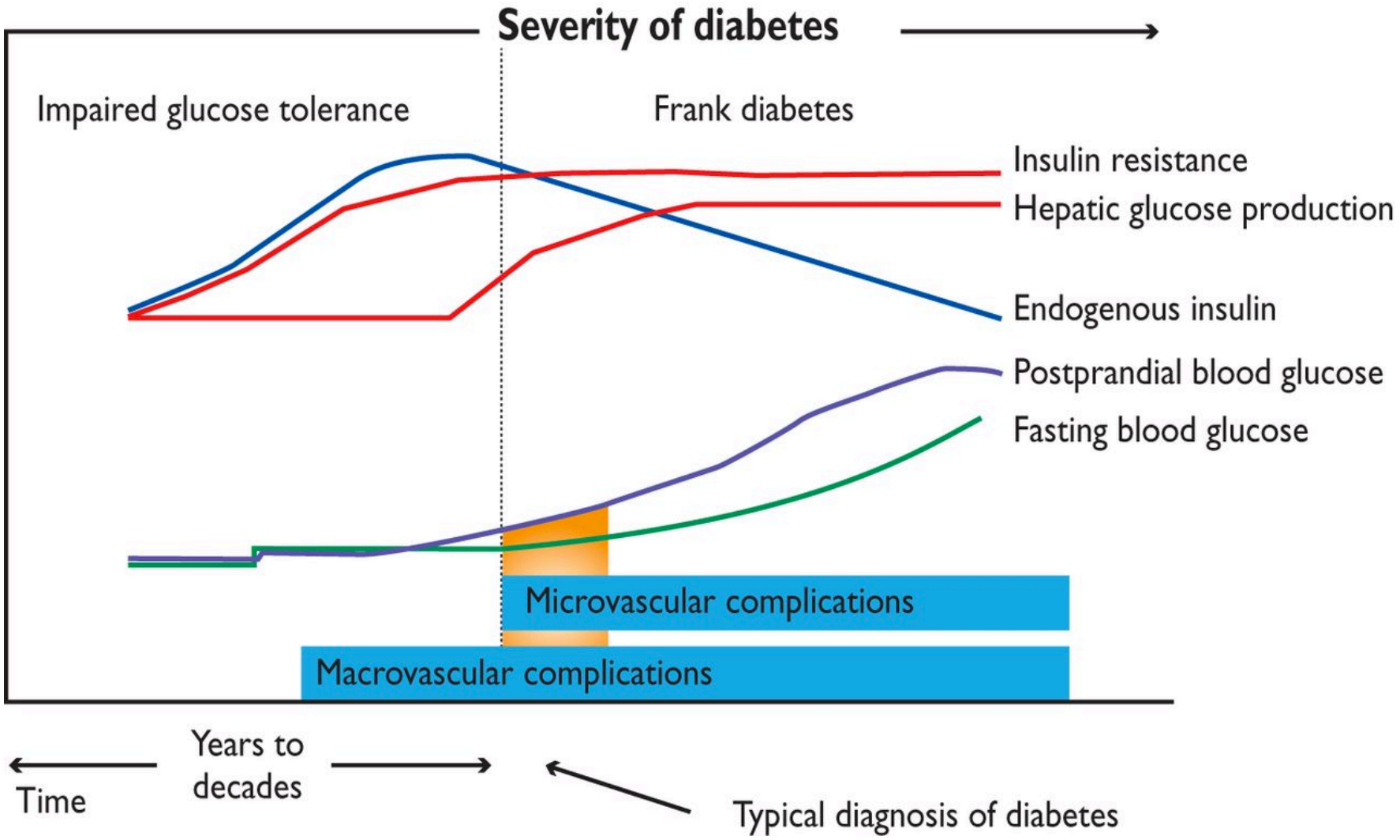
Densité par région en France en 2013*

Freestyle Libre sera réservé « *aux patients atteints d'un diabète de type 1 ou de type 2 (adultes et enfants âgés d'au moins 4 ans) traités par insulinothérapie intensifiée (par pompe externe ou ≥ 3 injections par jour) et pratiquant une autosurveillance glycémique pluriquotidienne (≥ 3/j).* »

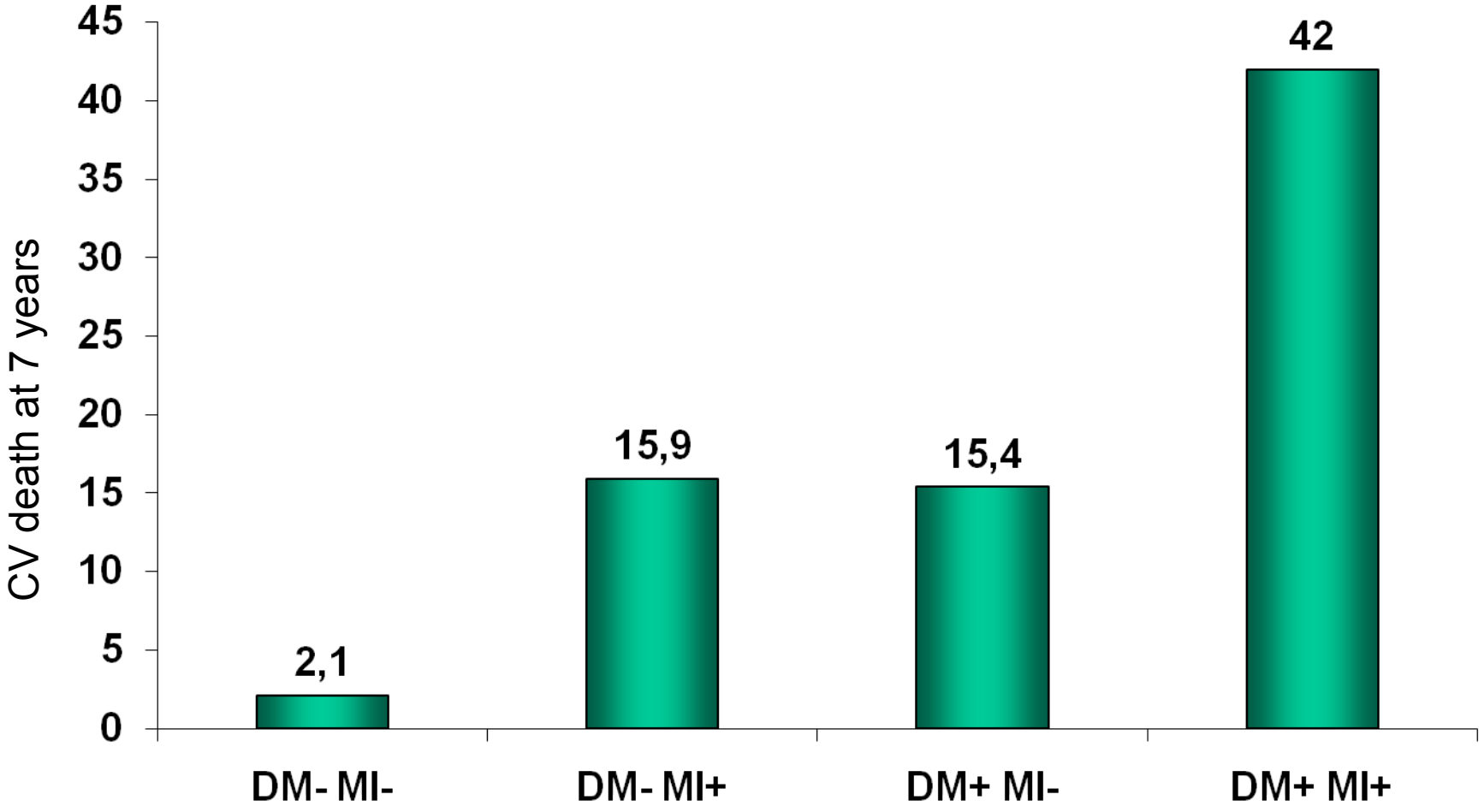
Principe général du fonctionnement d'un pancréas artificiel




REMEMBER
YOUR FIRST TIME WITH
YOUR INSULIN PUMP ...
Diabetic

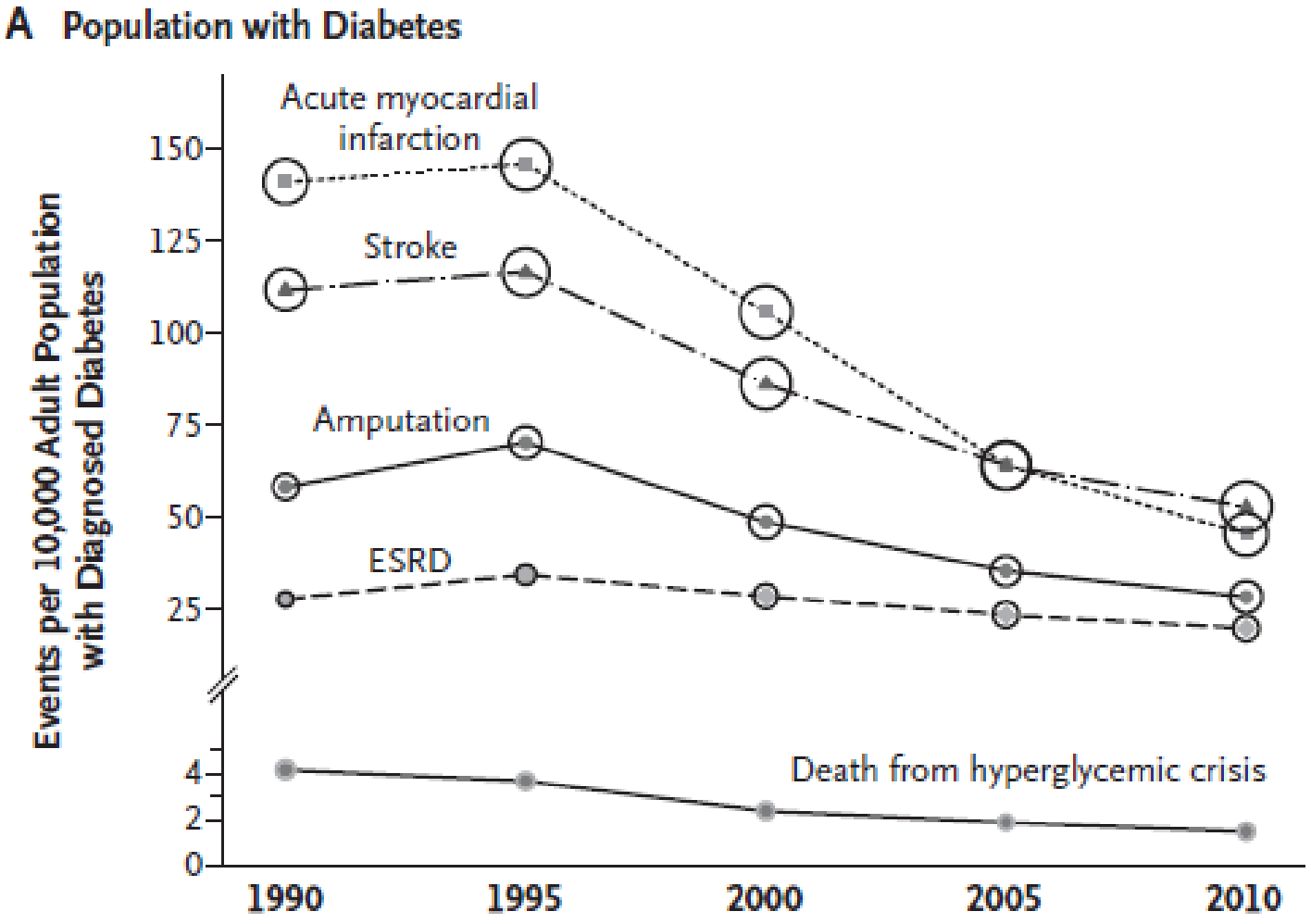

Severity of diabetes
Impaired glucose tolerance
Frank diabetes
Insulin resistance
Hepatic glucose production
Endogenous insulin
Postprandial blood glucose
Fasting blood glucose
Microvascular complications
Macrovascular complications
Time
Years to decades
Typical diagnosis of diabetes

CV risk in diabetes mellitus vs CAD



Haffner, 1998

Changes in Diabetes-Related Complications in the United States, 1990–2010



Gregg et al. N Engl J Med 2014;370:1514-23

BEH Bulletin épidémiologique hebdomadaire
InVS INSTITUT DE VEILLE SANITAIRE
N° 34-35 | 10 novembre 2015

Journée mondiale du diabète 2015.
Suivi du diabète et poids de ses complications sévères en France
// World Diabetes Day 2015.
Diabetes follow-up and burden of it's severe complications, in France

Tableau 1

Taux d'incidence standardisés[a] des complications liées au diabète, France entière, 2013

	Population diabétique (/100 000)	Population non diabétique (/100 000)	Indice comparatif d'incidence
Infarctus du myocarde	367	168	2,2
Accident vasculaire cérébral	470	301	1,6
Démarrage d'un traitement de suppléance pour insuffisance rénale chronique terminale[b]	91	10	9.2
Amputations d'un membre inférieur	232	33	7,0
Plaies du pied	610	123	5,0

[a] Standardisation sur la structure d'âge de la population européenne 2010 : Eurostat, population EU-27 chez les personnes âgées de plus de 45 ans.
[b] Standardisation sur la structure d'âge de la population européenne 2010 : Eurostat, population EU-27.

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Taux d'incidence standardisés[a] des complications liées au diabète selon le sexe, France entière, 2013

	Hommes (/100 000)	Femmes (/100 000)	Indice comparatif d'incidence
Infarctus du myocarde	469	236	2,0
Accident vasculaire cérébral	530	397	1,4
Démarrage d'un traitement de suppléance pour insuffisance rénale chronique terminale[b]	104	77	1,4
Amputations d'un membre inférieur	322	125	2,6
Plaies du pied	732	454	1,6

[a] Standardisation sur la structure d'âge de la population européenne 2010 : Eurostat, population EU-27 chez les personnes âgées de plus de 45 ans.
[b] Standardisation sur la structure d'âge de la population européenne 2010 : Eurostat, population EU-27.

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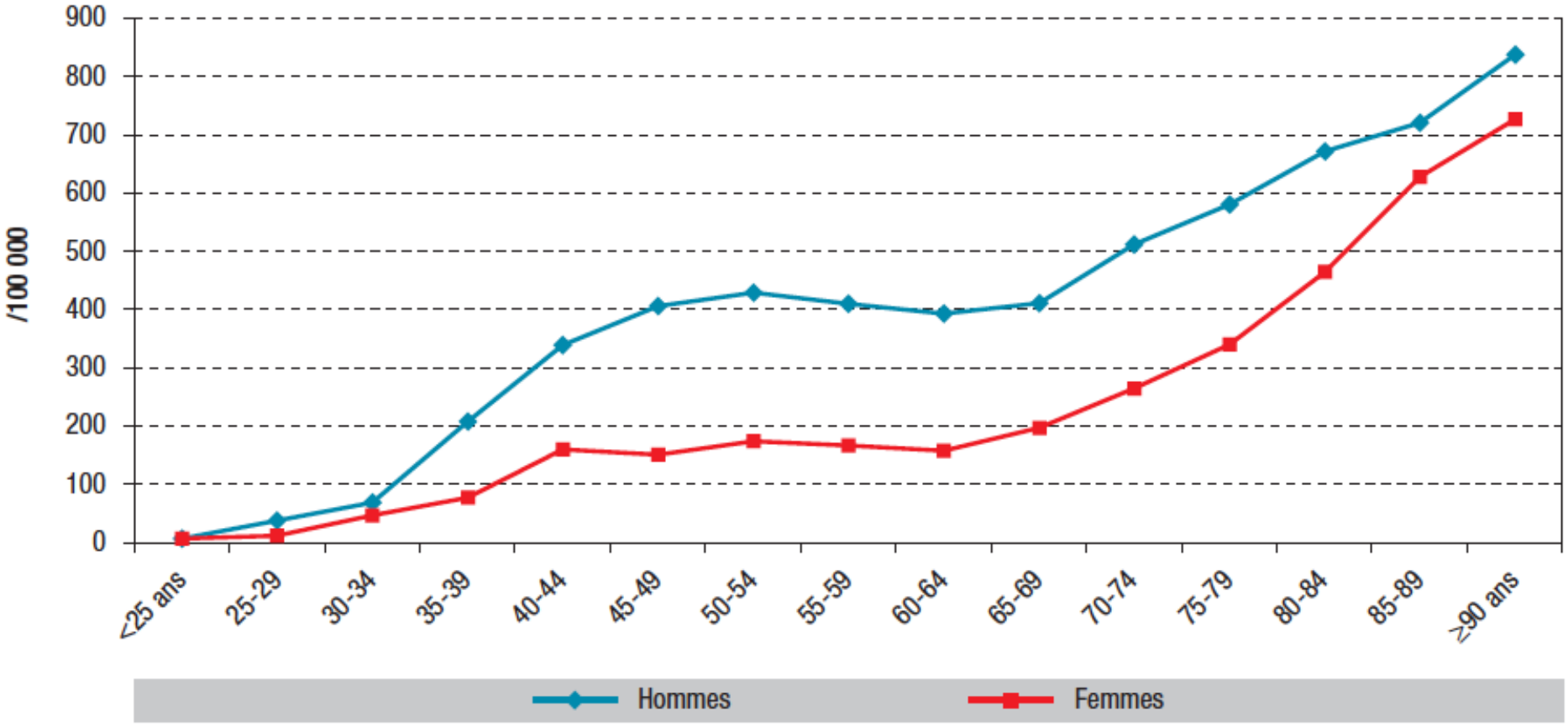
Taux de personnes diabétiques traitées pharmacologiquement hospitalisées pour infarctus du myocarde (pour 100 000 personnes diabétiques) selon le sexe et l'âge, France entière, 2013



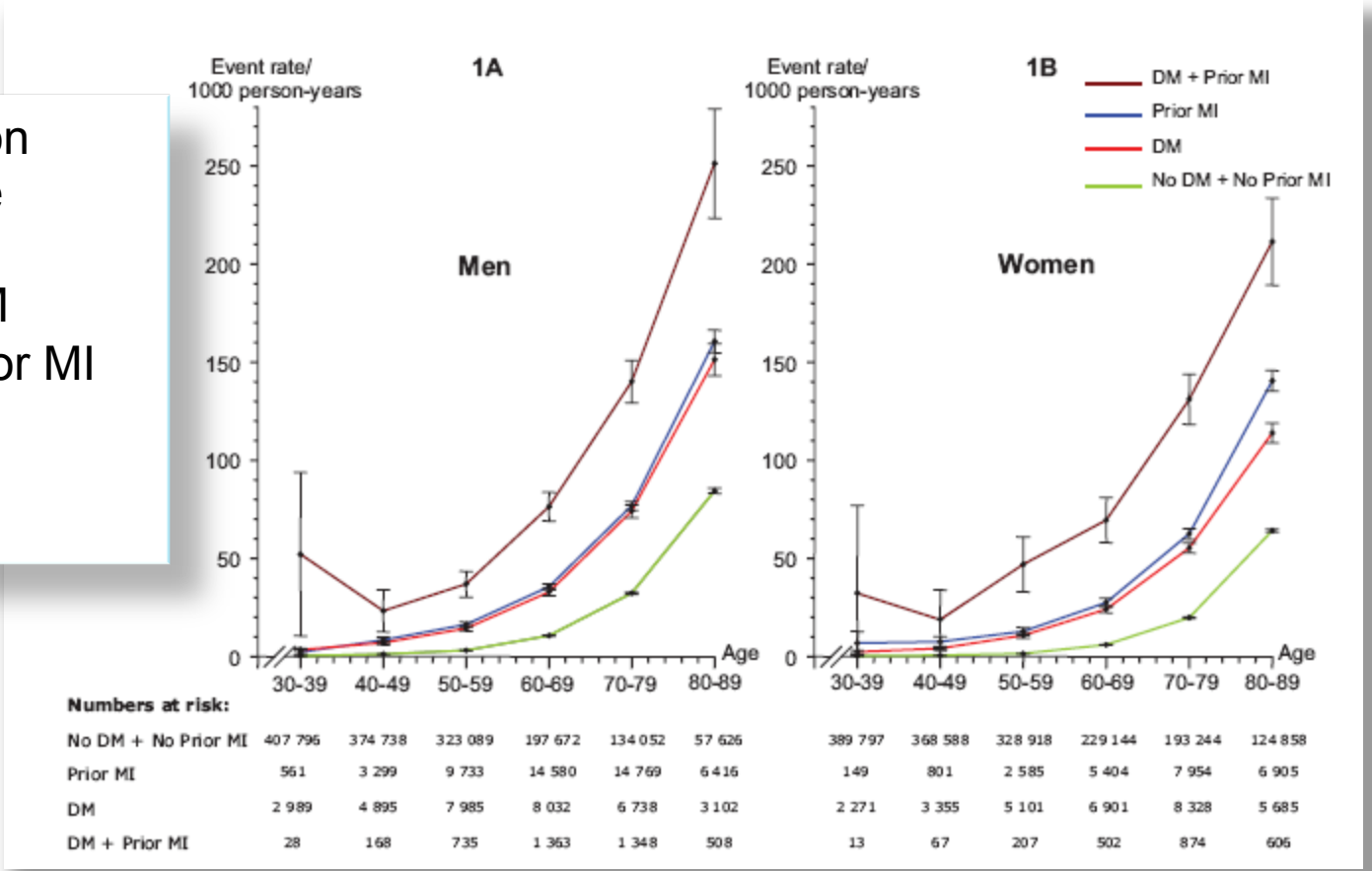
Champ : France entière (hors Mayotte). Sources : Sniiram, DCIR-PMSI.

Cardiovascular mortality in the Danish registry: role of diabetes and CAD

Danish population
≥30 years of age

- 71 801 with DM
- 79 575 with prior MI

Five-year F/U



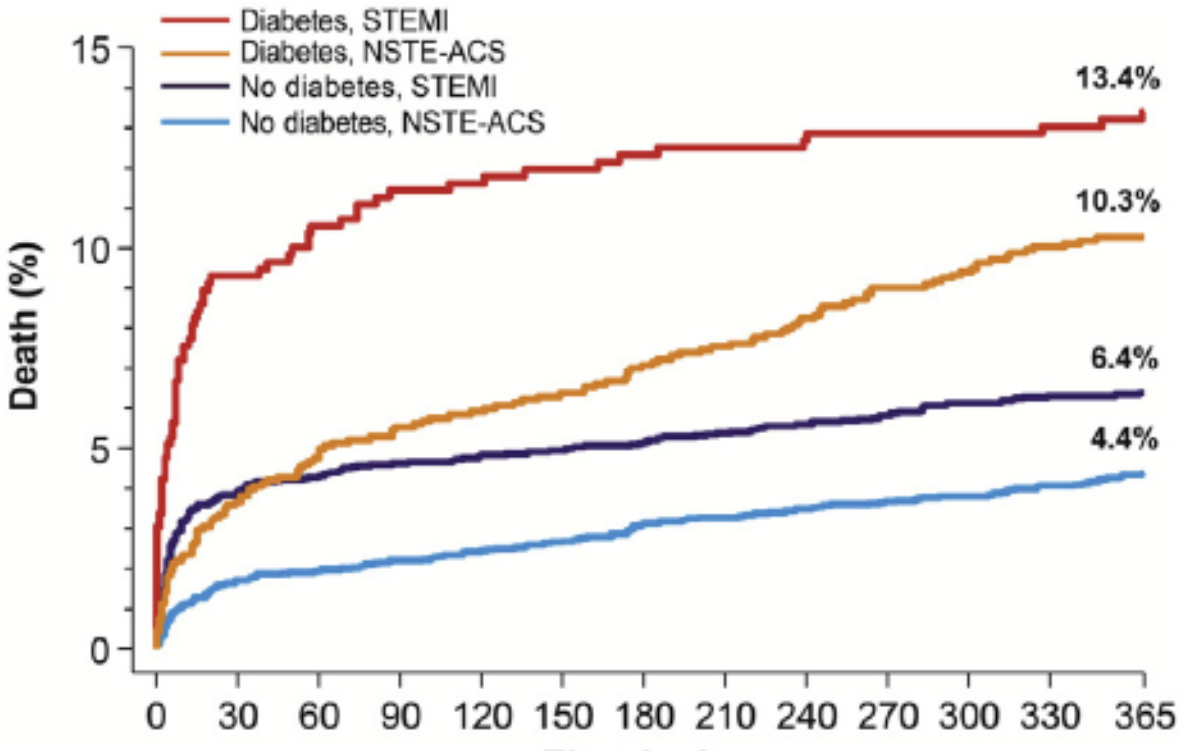
Schramm et al. Circulation 2008

Effect of Diabetes Mellitus on Frequency of Adverse Events in Patients With Acute Coronary Syndromes Undergoing Percutaneous Coronary Intervention

Raffaele Piccolo, MD[a], Anna Franzone, MD[a], Konstantinos C. Koskinas, MD[a], Lorenz Räber, MD, PhD[a], Thomas Pilgrim, MD[a], Marco Valgimigli, MD, PhD[a], Stefan Stortecky, MD[a], Julie Rat-Wirtzler, MSc[b], Sigmund Silber, MD[c], Patrick W. Serruys, MD[d], Peter Jüni, MD[e,f], Dik Heg, PhD[b,g], and Stephan Windecker, MD[a,*]

Few data are available on the timing of adverse events in relation to the status of diabetes mellitus and the type of acute coronary syndrome (ACS). We investigated this issue in diabetic and nondiabetic patients admitted with a diagnosis of non–ST-segment elevation ACS (NSTE-ACS) or ST-segment elevation myocardial infarction (STEMI) undergoing percutaneous coronary intervention. Patient-level data from 6 studies (n = 16,601) were pooled and only patients with ACS are included (n = 9,492). Early (0 to 30 days), late (31 to 365 days), and overall (0 to 365 days) events were analyzed. Diabetes mellitus was present in 1,927 patients (20.3%). At 1 year, all-cause mortality was highest for diabetic patients with STEMI (13.4%), followed by diabetic patients with NSTE-ACS (10.3%), nondiabetic patients with STEMI (6.4%) and nondiabetic patients with NSTE-ACS (4.4%; p <0.001). Among patients with diabetes, there was a significant interaction (p <0.001) for STEMI versus NSTE-ACS in early compared with late mortality, due to an excess of early mortality associated with STEMI (9.3% vs 3.7%; hazard ratio 2.31, 95% CI 1.52 to 3.54, p <0.001). Compared with diabetic NSTE-ACS patients, diabetic patients with STEMI had an increased risk of early stent thrombosis (hazard ratio 2.26, 95% CI 1.48 to 3.44, p <0.001), as well as a significant interaction (p = 0.009) in the risk of target lesion revascularization between the early and late follow-up. The distribution of fatal and nonfatal events according to the type of ACS was not influenced by diabetic status. In conclusion, diabetes in ACS setting confers a worse prognosis with 1-year mortality >10% in both STEMI and NSTE-ACS. Notwithstanding the high absolute rates, the temporal distribution of adverse events related to the type of ACS is similar between diabetic and nondiabetic patients. © 2016 Elsevier Inc. All rights reserved. (Am J Cardiol 2016;118:345–352)

Piccolo et al, Am J Cardiol 2016;118:345-52



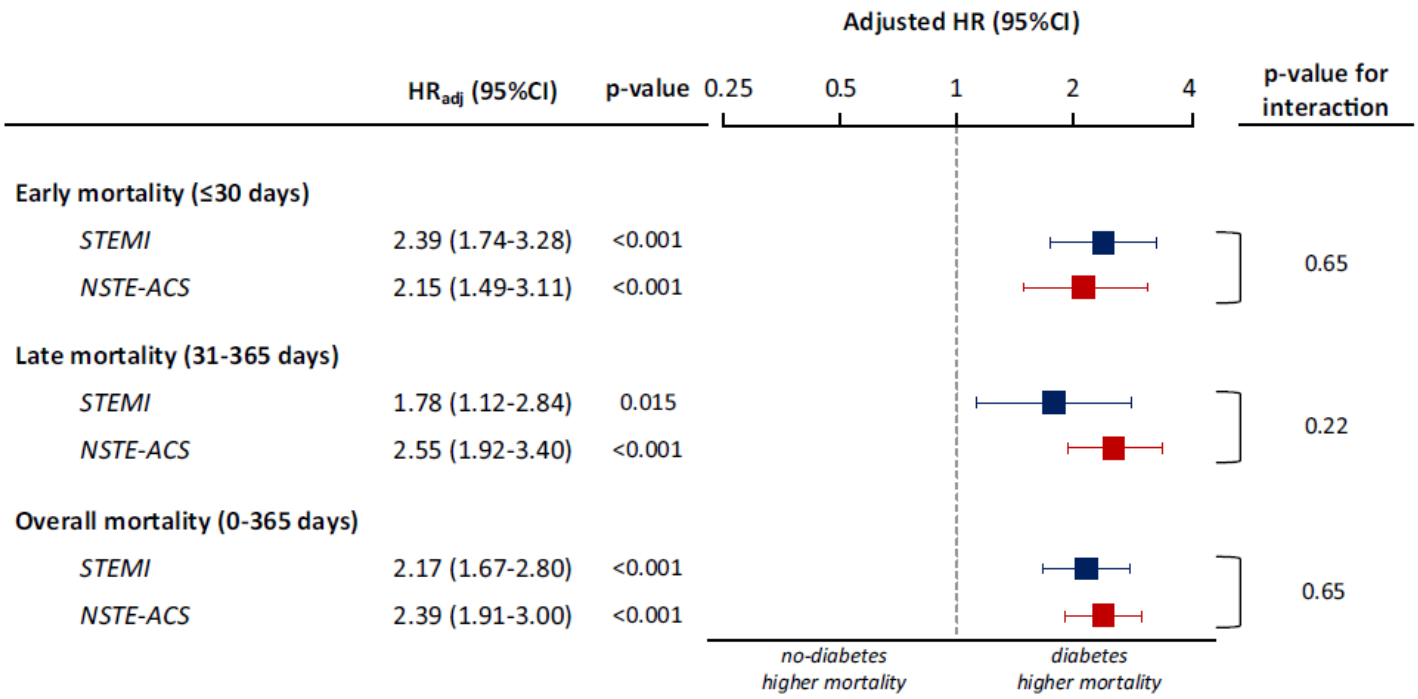
Number at risk

No diabetes, STEMI	3339	3092	3068	3054	3046	3041	3034	3022	3013	3006	2996	2987	2843
No diabetes, NSTE-ACS	4226	4027	4007	3996	3986	3976	3955	3941	3929	3922	3916	3901	3747
Diabetes, STEMI	591	514	504	498	497	495	491	490	489	488	488	486	462
Diabetes, NSTE-ACS	1336	1247	1229	1219	1213	1207	1197	1190	1181	1169	1163	1153	1100

Figure 1. Kaplan–Meier time-to-event curves showing all-cause mortality at 1 year across the 4 study groups.

Piccolo et al, Am J Cardiol 2016;118:345-52

Early, late, and overall mortality associated with diabetic status



Adjusted hazard ratios from Cox regressions comparing diabetes versus nondiabetes, stratified by trial and adjusted for age, gender, body mass index, hypertension, hypercholesterolemia, smoker; history of coronary artery disease, myocardial infarction.

Piccolo et al, Am J Cardiol 2016;118:345-52

Risque CV du diabétique

- Quel outil pour évaluer le risque cardio-vasculaire de vos diabétiques

1. Equations de risque
2. Recherche ischémie à l'effort
3. Score calcique
4. Impuissance
5. Protéinurie

Risque CV du diabétique

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5.6 Recommendations for cardiovascular risk assessment in diabetes

Cardiovascular risk assessment in diabetes			
Recommendations	**Class** [a]	**Level** [b]	**Ref.** [c]
It should be considered to classify patients with DM as at very high or high risk for CVD depending on the presence of concomitant risk factor and target organ damage.	IIa	C	-
It is not recommended to assess the risk for CVD in patients with DM based on risk scores developed for the general population.	III	C	-
It is indicated to estimate the urinary albumin excretion rate when performing risk stratification in patients with DM.	I	B	113
Screening for silent myocardial ischaemia may be considered in selected high risk patients with DM.	IIb	C	-

CVD = cardiovascular disease; DM = diabetes mellitus.

[a]Class of recommendation.

[b]Level of evidence.

[c]Reference(s) supporting levels of evidence.

EASD / ESC 2013

Dépister / visualiser la maladie coronaire

Fonctionnelle

- Ischémie lors d'une augmentation des besoins en oxygène
- La lésion doit être suffisamment sténosante pour induire une ischémie
- Ne prédit pas le risque de survenue d'un thrombus (infarctus)

Tout le monde	ECG Peu couteux Très peu sensible	13
Patient capable de faire un effort suffisant	Epreuve d'effort Peu couteux Niveau d'effort souvent insuffisant Peu spécifique (hypertrophie)	90
Patient pouvant faire un effort limité	Scintigraphie Sensible - quantification Disponibilité moyenne	480
Patient ne pouvant pas faire d'effort ou ne pouvant faire qu'un effort limité	Echographie de stress Sensible quantification Echogenicité Opérateur dépendant	170
Patient ne pouvant pas faire d'effort ou ne pouvant faire qu'un effort limité– seconde intention	IRM de stress Sensible quantification Disponibilité très faible	70
Evaluation fonctionnelle d'une lésion coronaire lors d'une coronarographie	FFR Sensible et spécifique Prix élevé	

Anatomique

- Visualise l'athérome
- Ne prédit pas le risque de survenue d'un thrombus (infarctus)

Score calcification Peu couteux Pas de contraste Définit un risque statistique 25	Première approche globale
Scanner coronaire Visualise athérome non sténosant Contraste Opérateur dépendant Disponibilité faible	Patient ayant un test fonctionnel litigieux ou bas risque
Coronarographie Examen de référence Invasif Contraste	Patient ayant une preuve d'ischémie

Biologique

- Peu spécifique
- Pourrait prédire le risque d'infarctus … sans date

CRPus Prédiction d'évènements Définit un risque statistique très peu précis Peu spécifique	Recherche d'une inflammation circulante corrélé avec la survenue d'évènements aigus

Comparaison EE Effort / Scinti

	CoroTDM +	CoroTDM NS	CoroTDM-
Epreuve d'effort +	0	1	1
Epreuve d'effort litigieuse	3	5	2
Epreuve d'effort -	4	16	16
Scintigraphie +	2	3	0
Scintigraphie -	5	19	19
Epreuve d'effort ou scintigraphie +	2	4	1
Epreuve d'effort et scintigraphie -	5	18	18
TOTAL	7	22	19

Henry et al, Données personnelles

Comparison of Cardiovascular Magnetic Resonance and Single-Photon Emission Computed Tomography in Women With Suspected Coronary Artery Disease From the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) Trial

John P. Greenwood, PhD; Manish Motwani, MB, ChB; Neil Maredia, MD; Julia M. Brown, MSc; Colin C. Everett, MSc; Jane Nixon, PhD; Petra Bijsterveld, MA; Catherine J. Dickinson, PhD; Stephen G. Ball, PhD; Sven Plein, PhD

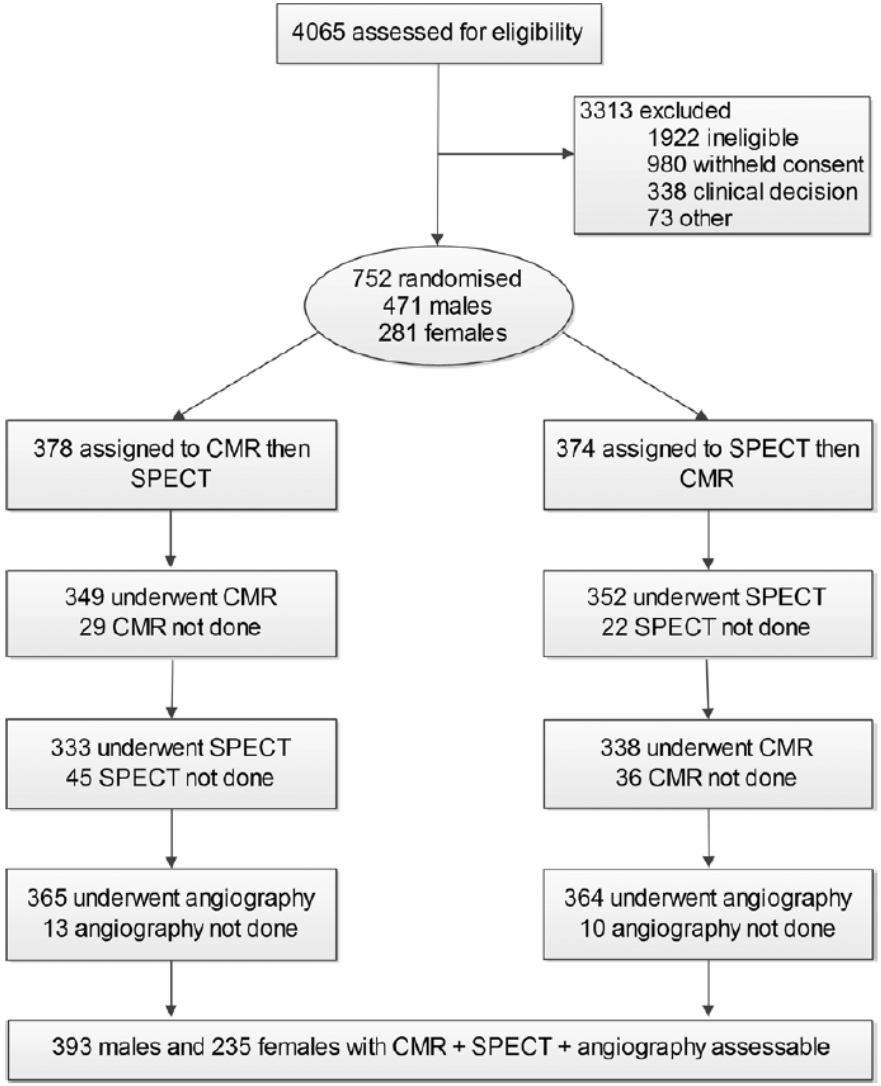
Background—Coronary artery disease is the leading cause of death in women, and underdiagnosis contributes to the high mortality. This study compared the sex-specific diagnostic performance of cardiovascular magnetic resonance (CMR) and single-photon emission computed tomography (SPECT).

Methods and Results—A total of 235 women and 393 men with suspected angina underwent CMR, SPECT, and x-ray angiography as part of the Clinical Evaluation of Magnetic Resonance Imaging in Coronary Heart Disease (CE-MARC) study. CMR comprised adenosine stress/rest perfusion, cine imaging, late gadolinium enhancement, and magnetic resonance coronary angiography. Gated adenosine stress/rest SPECT was performed with ^{99m}Tc-tetrofosmin. For CMR, the sensitivity in women and men was similar (88.7% versus 85.6%; P=0.57), as was the specificity (83.5% versus 82.8%; P=0.86). For SPECT, the sensitivity was significantly worse in women than in men (50.9% versus 70.8%; P=0.007), but the specificities were similar (84.1% versus 81.3%; P=0.48). The sensitivity in both the female and male groups was significantly higher with CMR than SPECT (P<0.0001 for both), but the specificity was similar (P=0.77 and P=1.00, respectively). For perfusion-only components, CMR outperformed SPECT in women (area under the curve, 0.90 versus 0.67; P<0.0001) and in men (area under the curve, 0.89 versus 0.74; P<0.0001). Diagnostic accuracy was similar in both sexes with perfusion CMR (P=1.00) but was significantly worse in women with SPECT (P<0.0001).

Conclusions—In both sexes, CMR has greater sensitivity than SPECT. Unlike SPECT, there are no significant sex differences in the diagnostic performance of CMR. These findings, plus an absence of ionizing radiation exposure, mean that CMR should be more widely adopted in women with suspected coronary artery disease.

Clinical Trial Registration—URL: http://www.controlled-trials.com. Unique identifier: ISRCTN77246133.

(*Circulation*. 2014;129:1129-1138.)



Greenwood et al, Circulation 2014

Table 4. Diagnostic Performance of Multicomponent CMR and SPECT for the Detection of CAD

	SPECT, %				Multicomponent CMR, %			
	Sensitivity	Specificity	PPV	NPV	Sensitivity	Specificity	PPV	NPV
Women (n=235)	50.9 (37.9–63.9)	84.1 (78.1–88.7)	48.2 (35.7–61.0)	85.5 (79.6–89.9)	88.7 (77.4–94.7)	83.5 (77.4–88.2)	61.0 (49.9–71.2)	96.2 (92.0–98.2)
Men (n=393)	70.8 (64.0–76.7)	81.3 (75.3–86.1)	78.9 (72.2–84.3)	73.9 (67.6–79.2)	85.6 (80.0–89.9)	82.8 (77.0–87.4)	83.1 (77.3–87.6)	85.4 (79.7–89.7)

When sensitivity and specificity of CMR and SPECT were compared in the same patients, the sample size is the n value given. When the sensitivity and specificity of 1 test in 1 sex are compared with those in the other sex, the sample size is the sum of the relevant n values. Significant CAD was defined as ≥70% luminal stenosis of a first-order coronary artery or left main stem stenosis ≥50% by quantitative coronary angiography. Values in parentheses are 95% confidence intervals. CAD indicates coronary artery disease; CMR, cardiovascular magnetic resonance; MVD, multivessel disease; NPV, negative predictive value; PPV, positive predictive value; SPECT, single-photon emission computed tomography; and SVD, single-vessel disease.

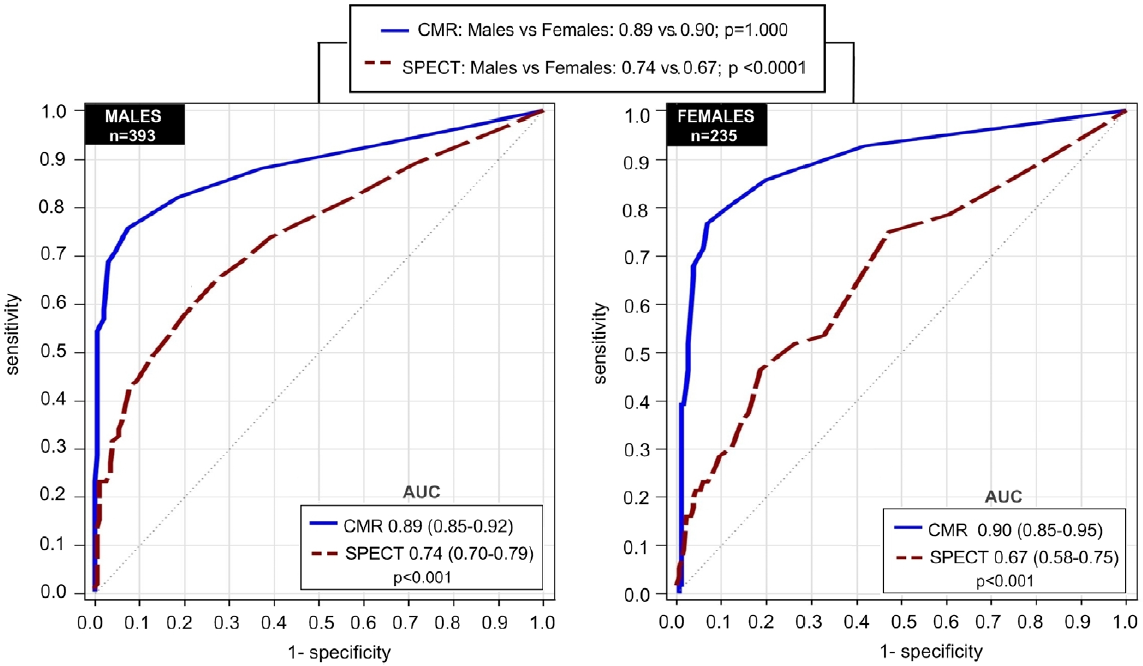
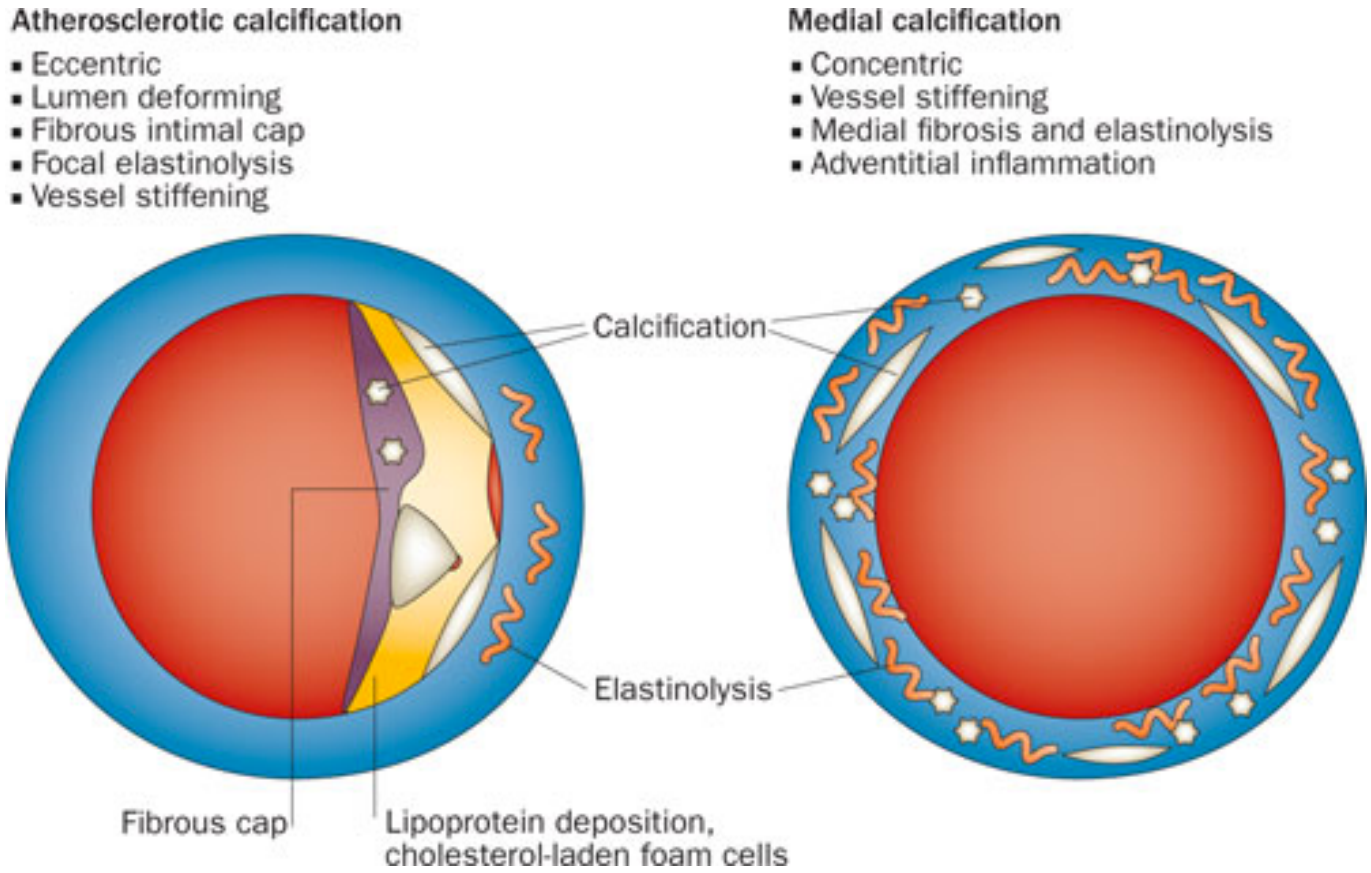
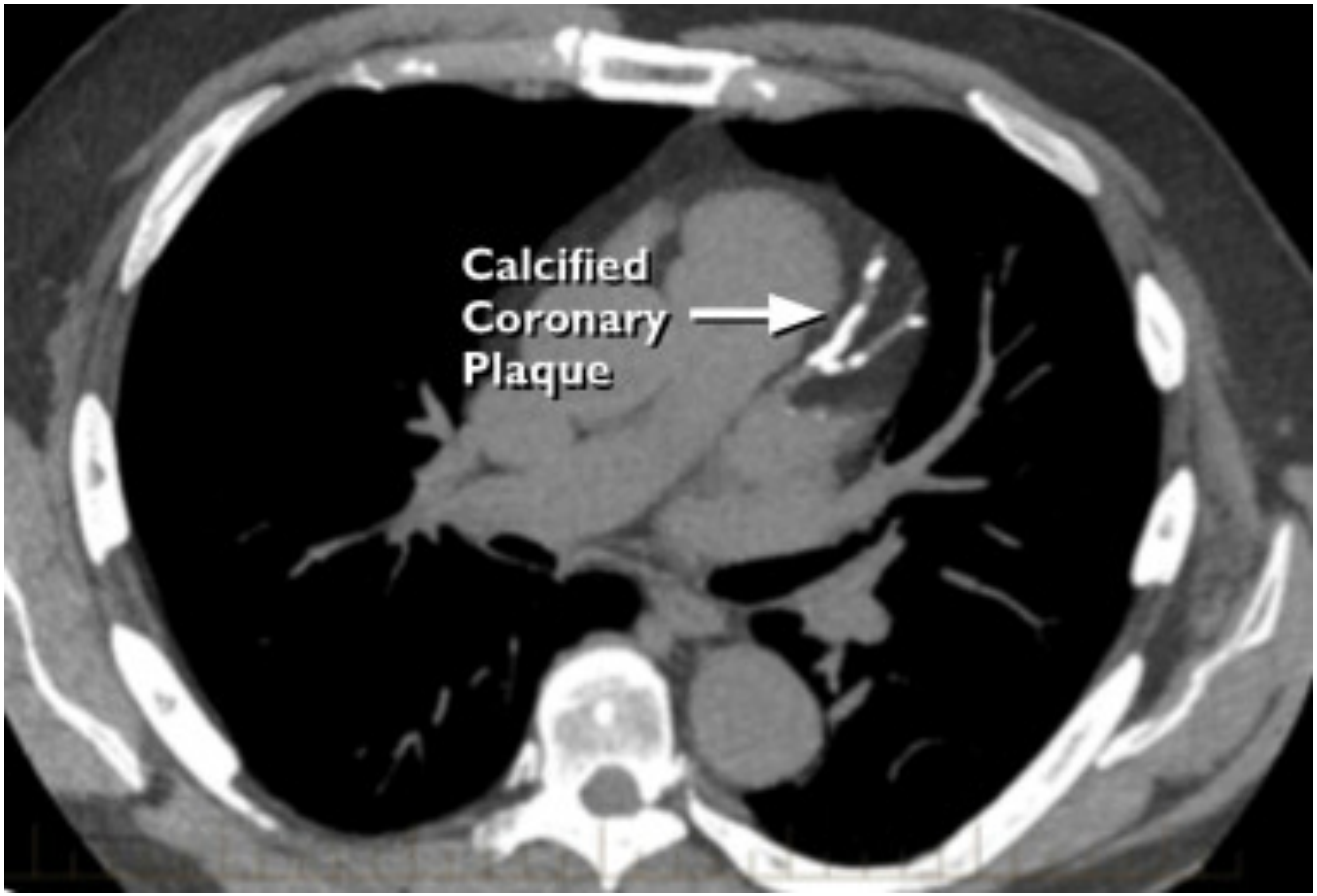


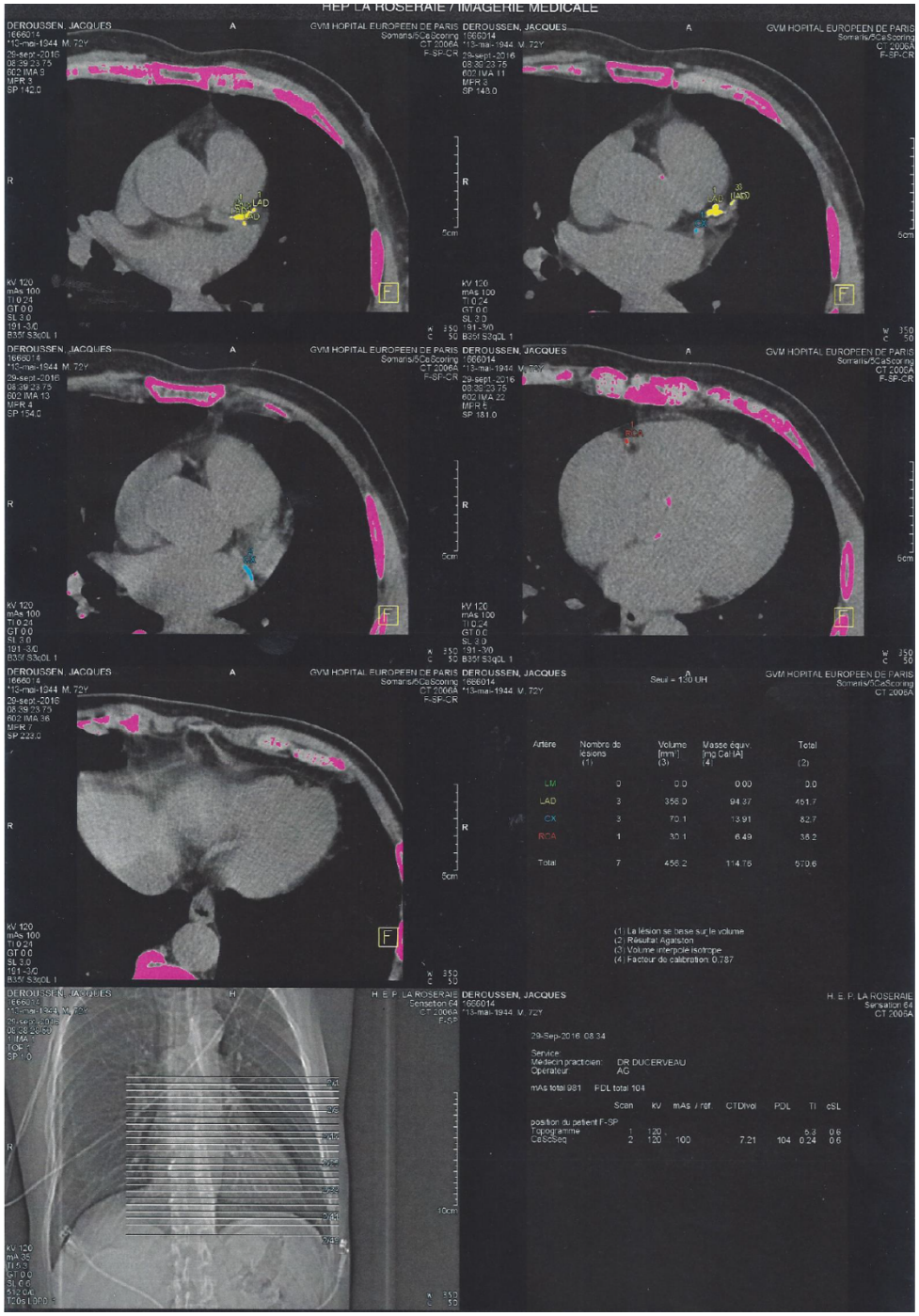
Figure 2. Receiver-operating characteristic (ROC) curves divided by sex. ROC curves generated with summed stress scores (n=393 men, 235 women). The diagnostic accuracy of stress perfusion cardiovascular magnetic resonance (CMR) was significantly greater than that of single-photon emission computed tomography (SPECT) in both sexes. For CMR, there was no significant difference in the diagnostic accuracy between men and women; with SPECT, there was a sex discrepancy with significantly worse performance in women. AUC indicates area under the curve.

Greenwood et al, Circulation 2014

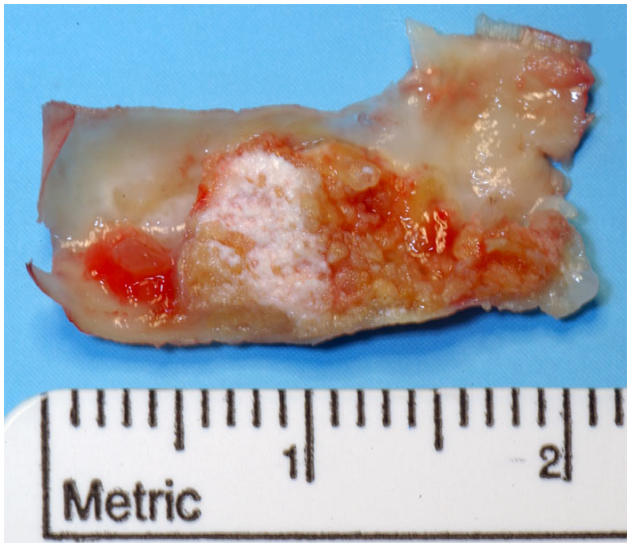
Score Calcique




Calcified
Coronary
Plaque



Score calcique



Score d'agatston

< 10

< 100

100 – 400

> 400

> 1000

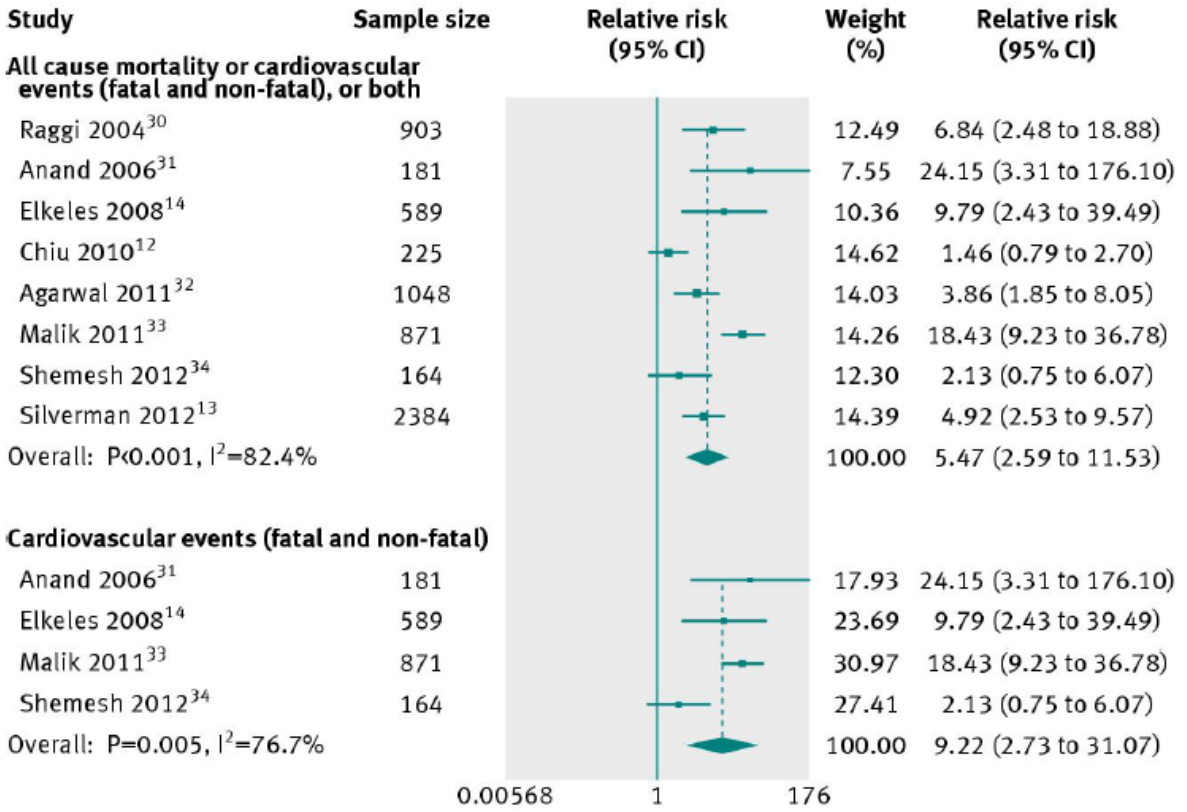
Score calcique

Table 3| **Meta-analysis comparing risk of all cause mortality or cardiovascular events, or both at different thresholds of coronary artery calcium (CAC) score in people with type 2 diabetes**

Thresholds of CAC score evaluated	No of studies	No of participants evaluated	Relative risk (95% CI)	I^2	Sensitivity (95% CI)	Specificity (95% CI)	Positive likelihood ratio (95% CI)	Negative likelihood ratio (95% CI)
CAC score <10 as reference group:								
Score ≥100 *v* <10	6	3014	8.4 (2.9 to 24.4)	86.9	94 (88 to 97)	43 (30 to 57)	1.7 (1.3 to 2.1)	0.1 (0.06 to 0.3)
Score ≥400 *v* <10	5	1573	13.2 (3.3 to 53.8)	89.3	90 (78 to 96)	70 (57 to 81)	3.0 (1.9 to 4.9)	0.1 (0.05 to 0.3)
Score ≥1000 *v* <10	4	1261	13.8 (5.4 to 34.9)	52.9	90 (82 to 95)	74 (50 to 89)	3.5 (1.6 to 7.6)	0.1 (0.07 to 0.2)
CAC score <100 as reference group:								
Score ≥100 *v* <100	7	6392	3.4 (2.4 to 4.8)	78.3	75 (67 to 82)	58 (46 to 70)	1.8 (1.4 to 2.4)	0.4 (0.3 to 0.5)
Score ≥400 *v* <100	5	2344	4.7 (2.5 to 9.0)	88.1	63 (52 to 72)	80 (66 to 90)	3.3 (1.7 to 6.3)	0.4 (0.3 to 0.6)
Score ≥1000 *v* <100	4	2757	7.3 (3.0 to 17.7)	87.2	66 (51 to 79)	85 (64 to 95)	4.4 (1.8 to 10.1)	0.4 (0.3 to 0.6)

Kramer et al, BMJ 2013

Score calcique >= 10



5,47

9,22

Fig 2 Meta-analyses of association between coronary artery calcium score ≥10 and outcome in people with type 2 diabetes. Weights are from random effects analysis

Kramer et al, BMJ 2013

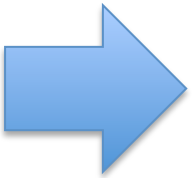
Score calcique

Est-ce qu'il n'y a pas d'athérome ?

Est-ce qu'il existe des plaques non serrées ?

Est-ce qu'il existe des plaques serrées ?

Est-ce qu'il existe des plaques instables ?



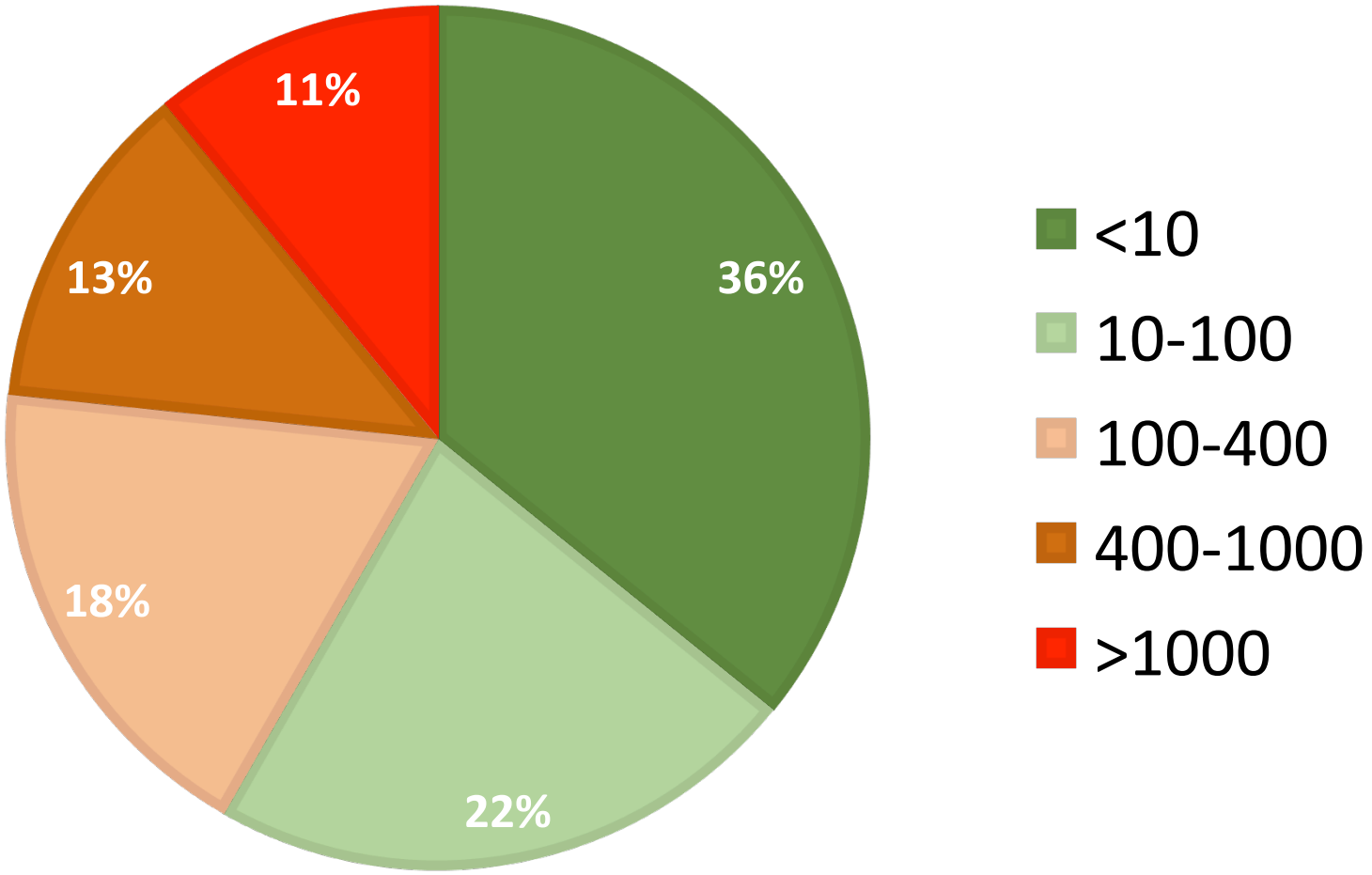
Recommendations for imaging methods

Recommendations	Class[a]	Level[b]	Ref[c]
Coronary artery calcium scoring may be considered as a risk modifier in CV risk assessment.	IIb	B	120–125
Atherosclerotic plaque detection by carotid artery scanning may be considered as a risk modifier in CV risk assessment.	IIb	B	126–128
ABI may be considered as a risk modifier in CV risk assessment.	IIb	B	129–132
Carotid ultrasound IMT screening for CV risk assessment is not recommended.	III	A	128, 133

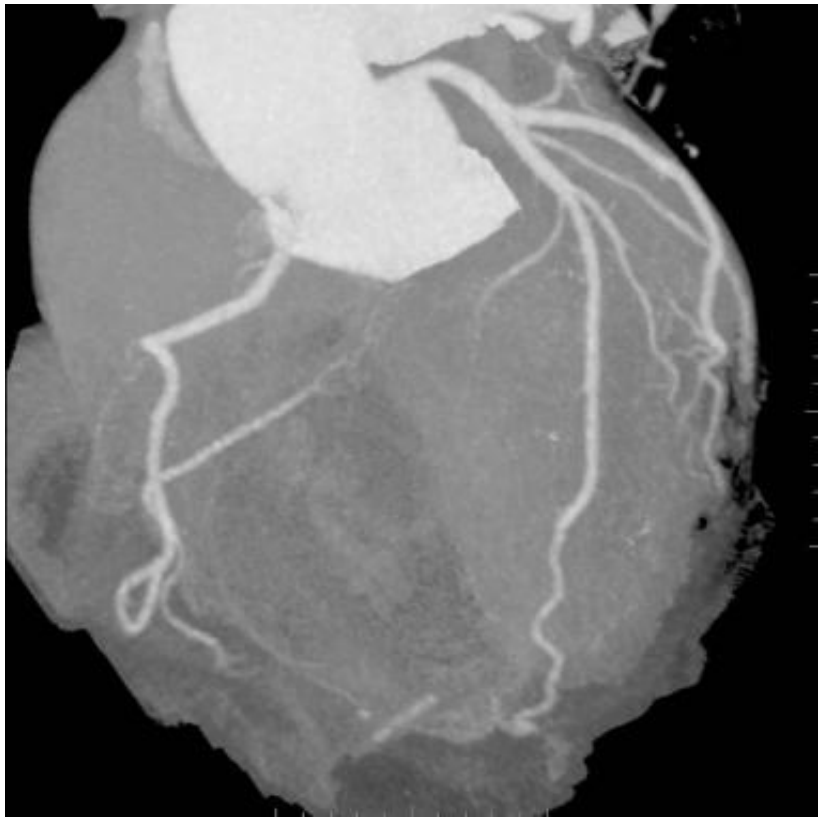
ABI = ankle–brachial index; CV = cardiovascular; IMT = intima–media thickness.
[a]Class of recommendation.
[b]Level of evidence.
[c]Reference(s) supporting recommendations.

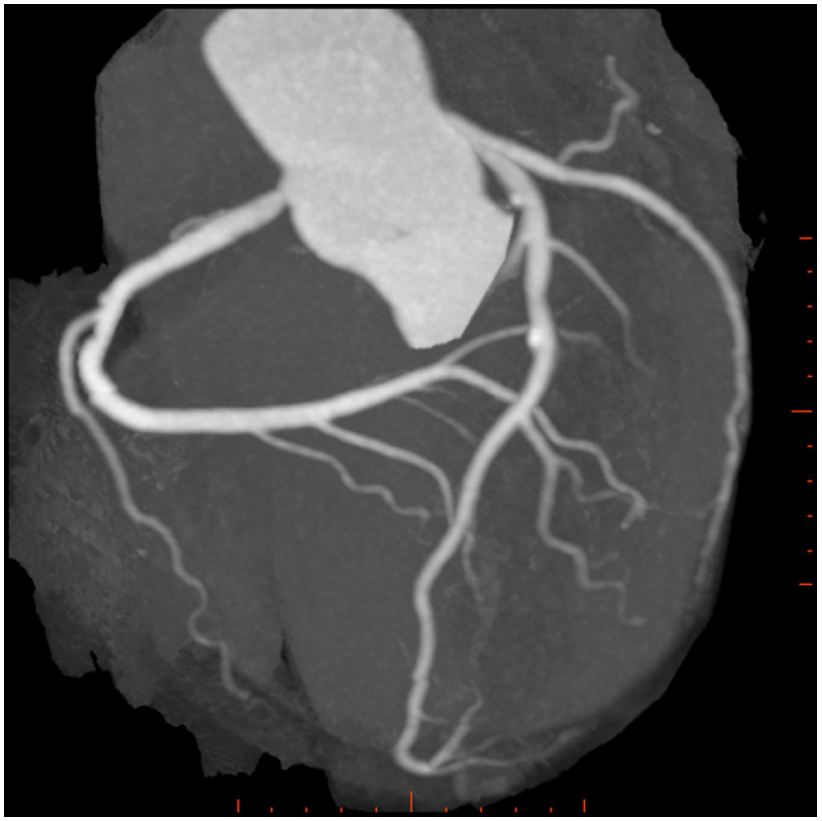
ESC prevention guidelines 2016

321 SCORES CALCIQUES REALISES A LARIBOISIERE CHEZ DES DIABÉTIQUES



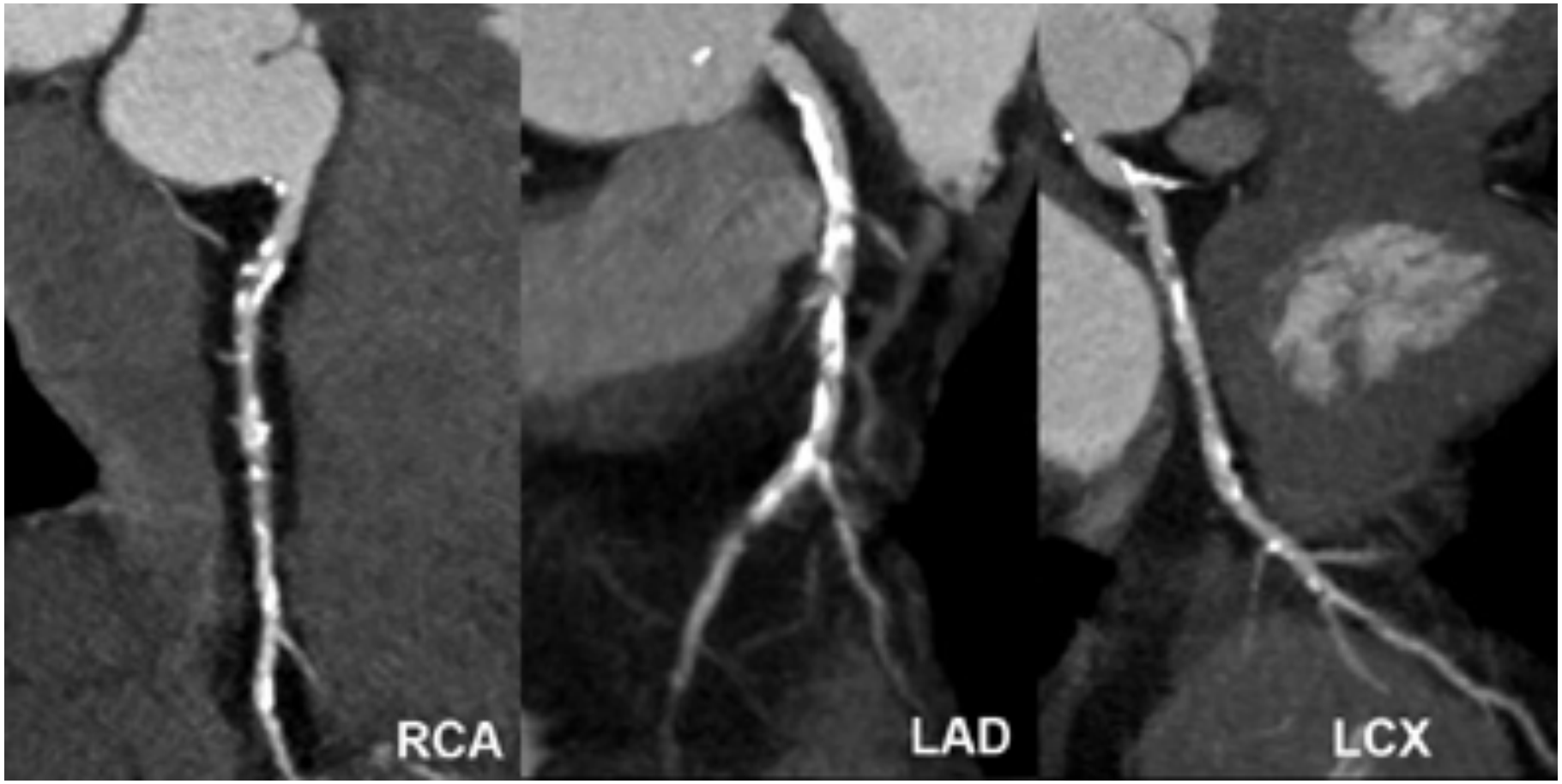
Scanner coronaire





Injection iode

Scanner coronaire



Protocole

- 3 / 4 Critères
  - Diabete type 2 > 10 ans
  - Diabète de type 1 de plus de 20 ancienneté
  - Age Femme > 60 – Homme > 55 ans
  - Microalbuminurie
  - Tabac
  - Tour de taille > 102 cm chez l'homme – 88 cm chez la femme
  - HTA (PA 140 ou 90) ou HTA traitée
  - LDL > 1.30 g/l ou tt par statine
  - HDL < 0.30 g/l
  - TG > 2.00 g/l
  - SAS documenté
  - Accident présumé coronaire chez un apparenté du premier degré chez quelqu'un de moins de 55 ans
  - VIH
  - Absence totale d érections matinales
  - ACFA

> Score de calcification

- Macroproteinurie
- Clairance creat < 45 ml/min
- Doute sur angor
- Modifs ECG – onde Q – Troubles repolarisation lateral
- Evènement clinique AVC AIT Claudication clinique
- Toute sténose > 50%
- Anévrysme aorte documenté
- Score de calcification > 100

> Scinti / IRM / ETT Stress

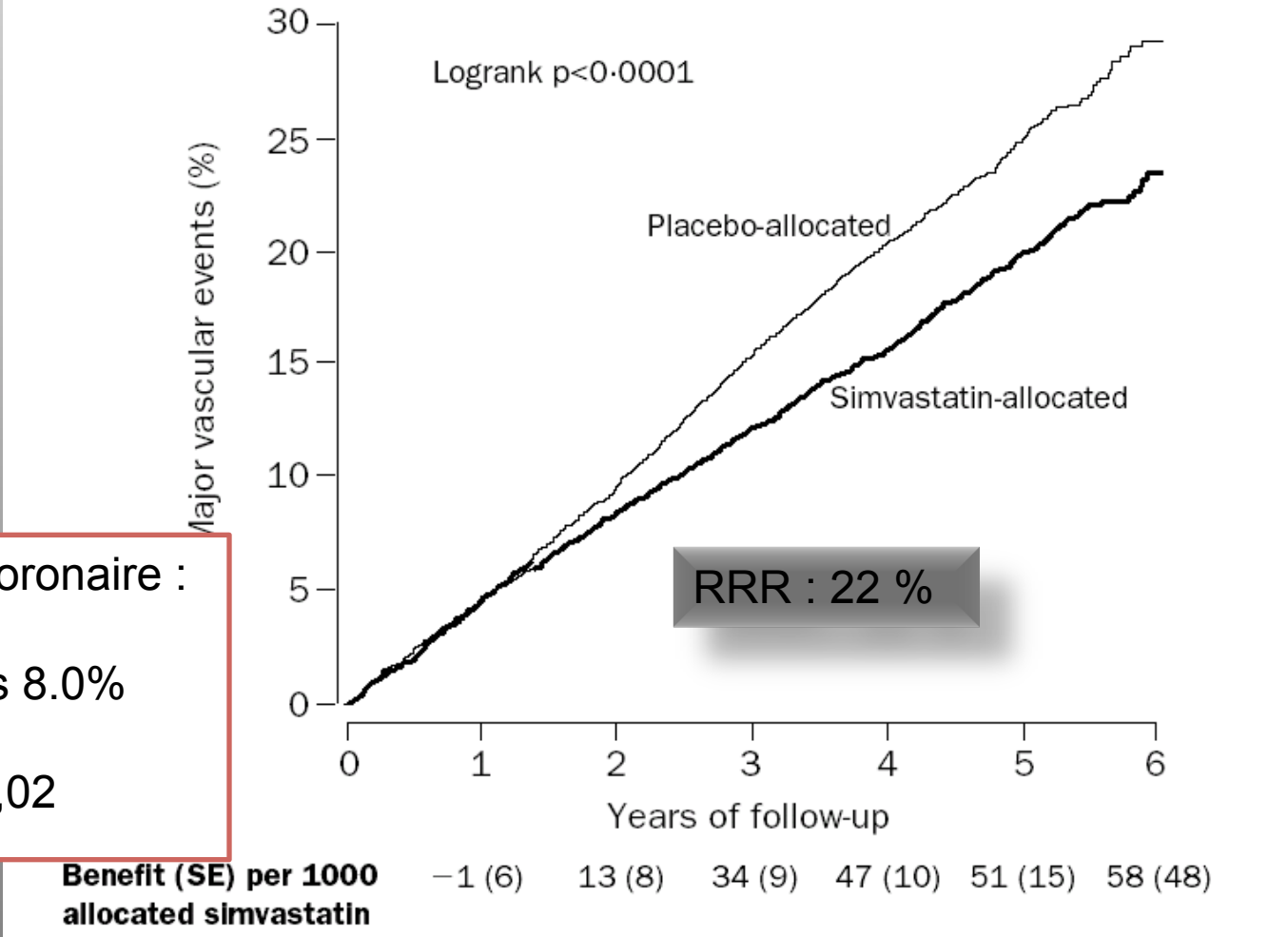
Quel est l'élément dont la correction est probablement la plus utile pour améliorer le pronostic CV du diabète

1. Glycemie instantanée
2. HbA1C
3. LDLc
4. PAS
5. PAD

Quel est l'élément dont la correction est probablement la plus utile pour améliorer le pronostic CV du diabète

1. Glycemie instantanée
2. HbA1C
3. LDLc
4. PAS
5. PAD

HPS: major events in diabetic patients



Mortalité coronaire :

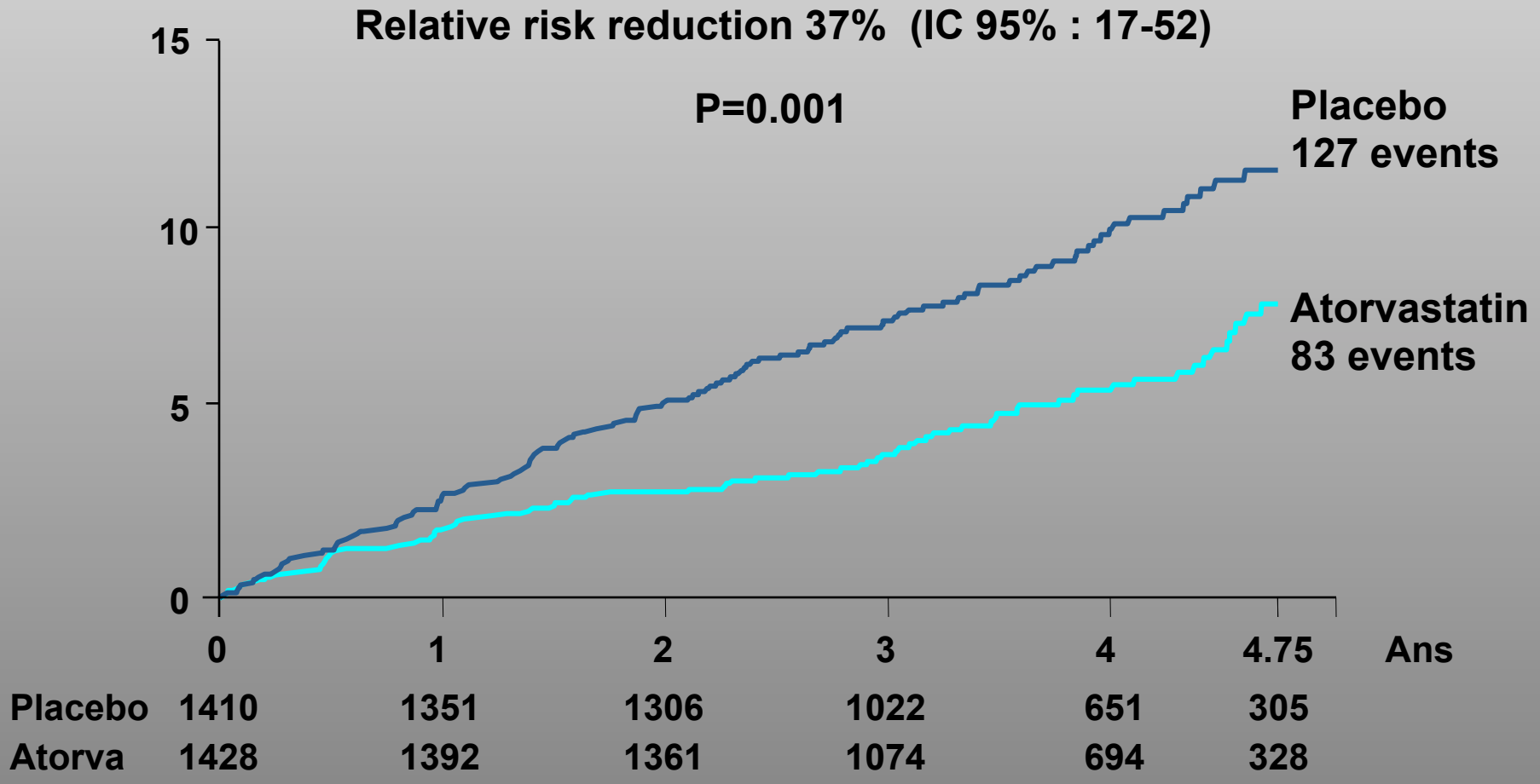
6.5% vs 8.0%

p=0,02

Lancet 2003 ; 361 : 2005

CARDS trial: primary end-point

CAD death, AMI, stroke, RCA, revascularisation, admission for unstable angina



HR overall mortality: 0.73; 95%CI: 0.52-1.01

Lancet 2004

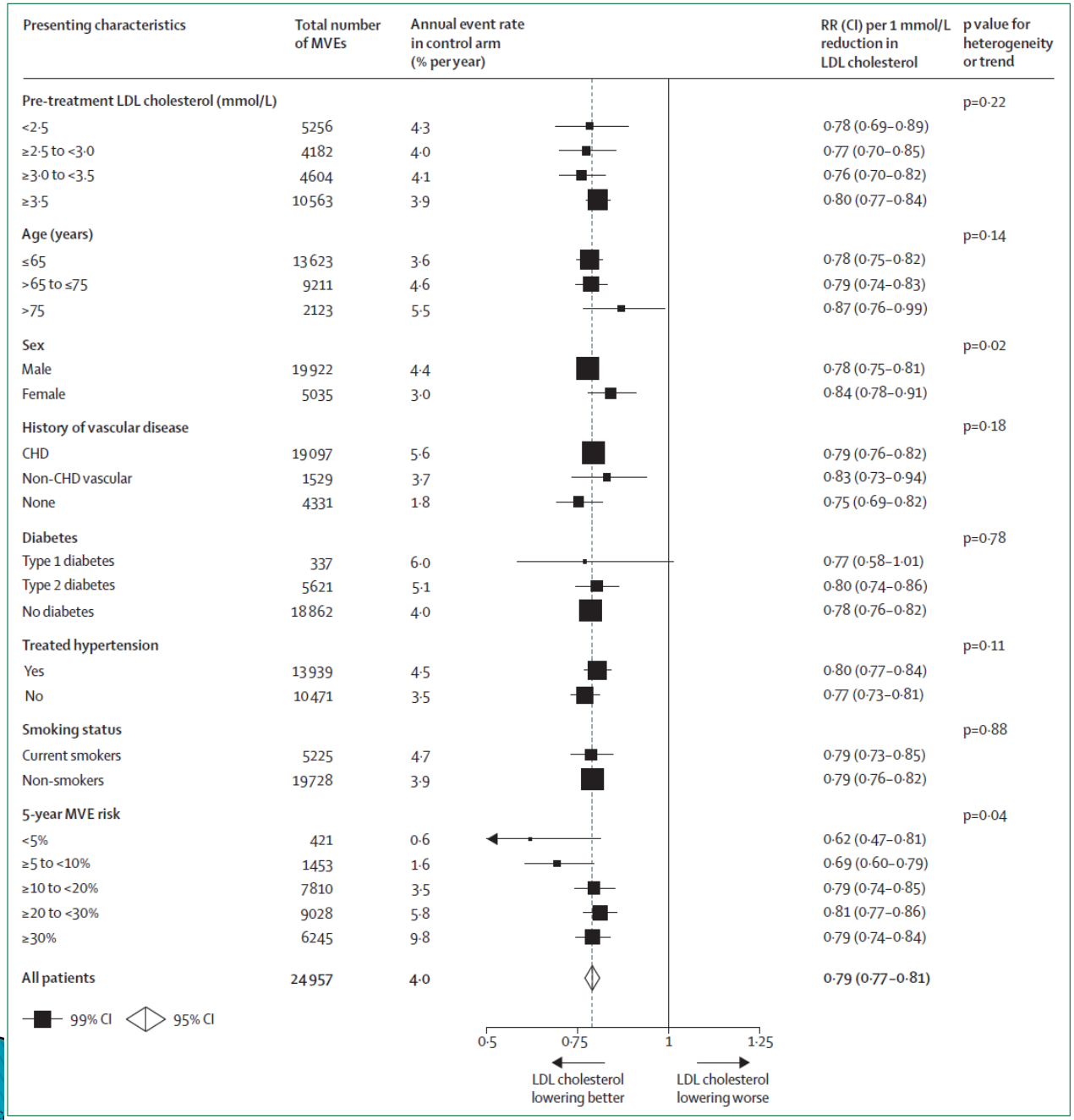


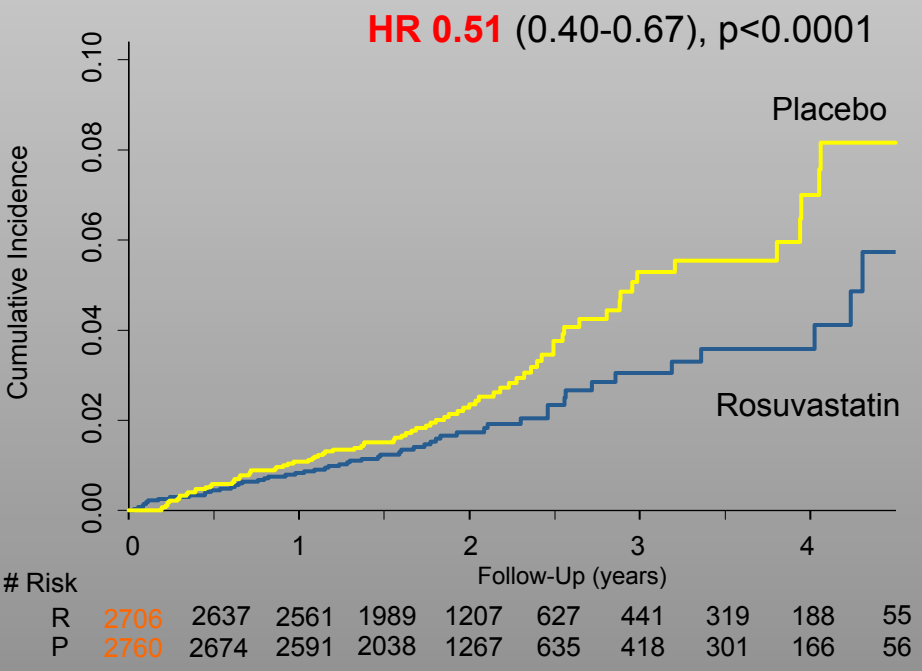
Figure 1: Similar proportional reductions in risks of major vascular events per mmol/L LDL cholesterol reduction in randomised trials of statin therapy among people with different presenting characteristics

Collins et al, Lancet 2016; 2332-61

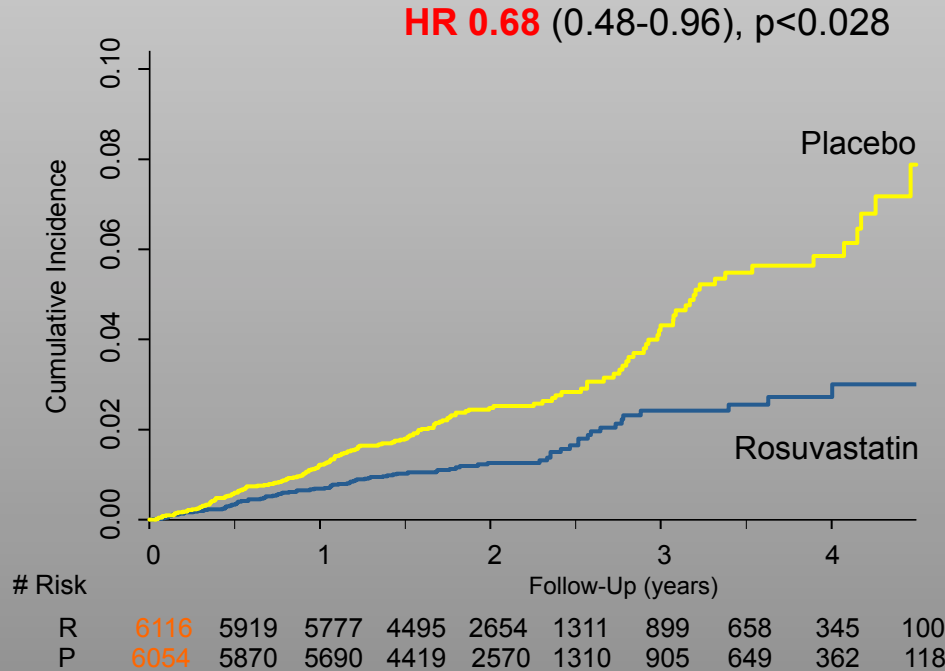
JUPITER : *Pre diabetic patients*

CV Events

Normal Glucose



Elevated glucose



Pradhan A *et al*. Circulation 2009; **120** (Suppl): S500; Abs 1425

Statines et risque de diabète

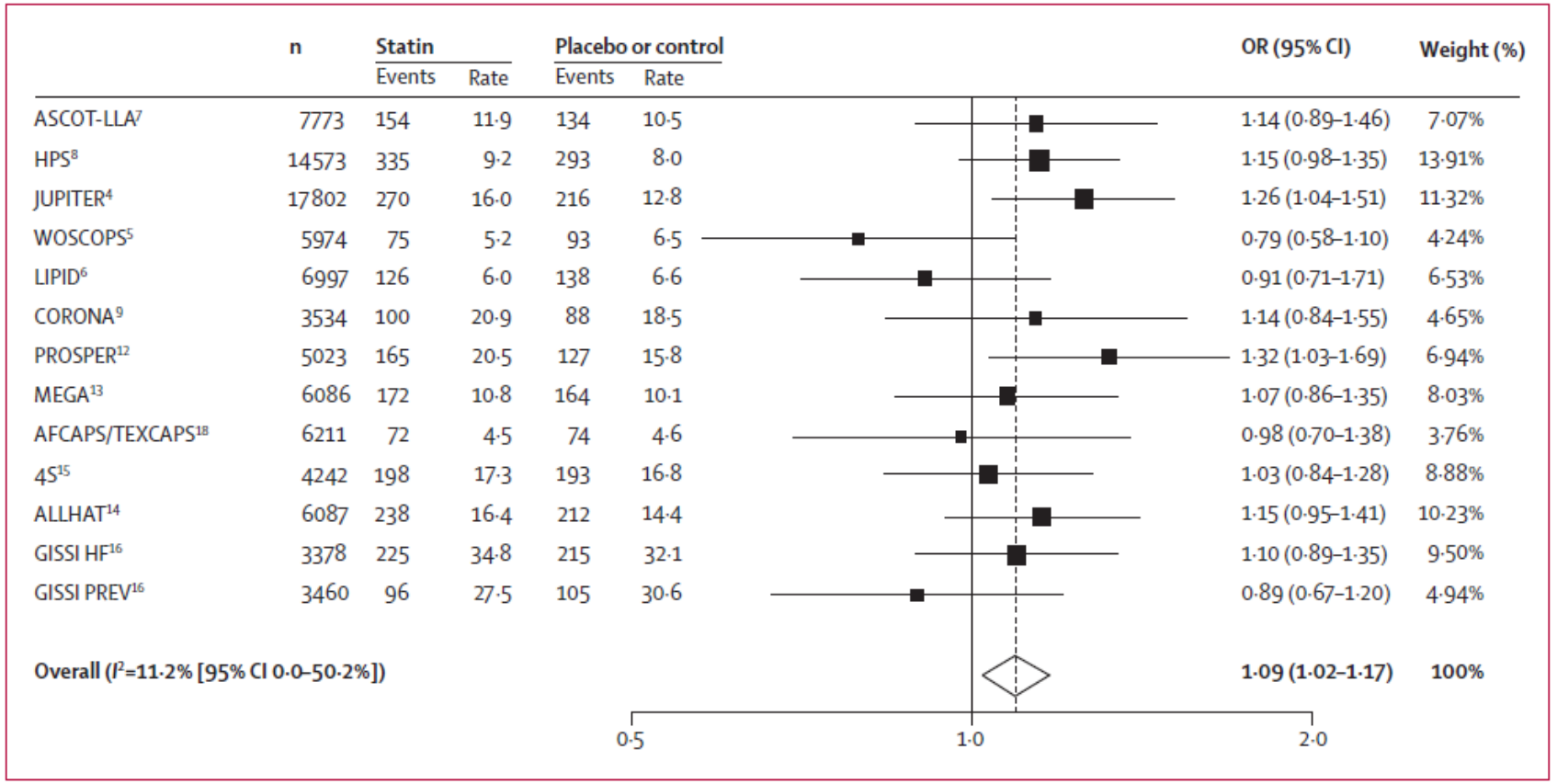


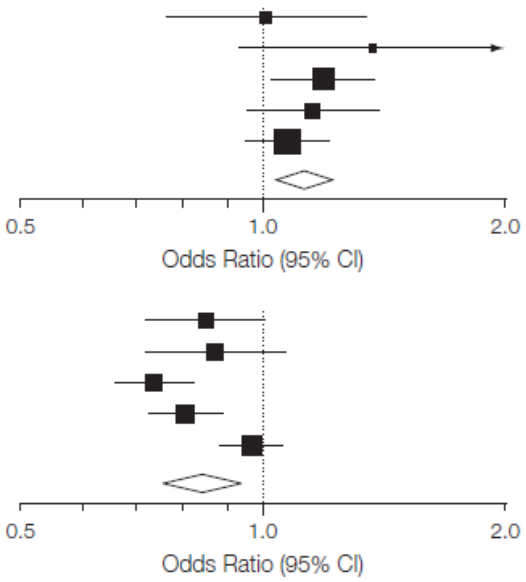
Figure 2: **Association between statin therapy and incident diabetes in 13 major cardiovascular trials†**
*Events per 1000 patient-years. †Weights are from random-effects analysis.

Lancet 2010

Statines et diabète – intensif vs. conventionnel

Figure 2. Meta-analysis of New-Onset Diabetes and First Major Cardiovascular Events in 5 Large Trials Comparing Intensive-Dose to Moderate-Dose Statin Therapy

	Cases/Total, No. (%)		
	Intensive Dose	Moderate Dose	OR (95% CI)
Incident Diabetes			
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,[5] 2010	625/5398 (11.6)	587/5399 (10.9)	1.07 (0.95-1.21)
Pooled odds ratio	**1449/16 408 (8.8)**	**1300/16 344 (8.0)**	**1.12 (1.04-1.22)**
Heterogeneity: $I^2 = 0\%$; $P = .60$			
Incident CVD			
PROVE IT–TIMI 22,[18] 2004	315/1707 (18.4)	355/1688 (21.0)	0.85 (0.72-1.01)
A to Z,[17] 2004	212/1768 (12.0)	234/1736 (13.5)	0.87 (0.72-1.07)
TNT,[15] 2005	647/3798 (17.0)	830/3797 (21.9)	0.73 (0.65-0.82)
IDEAL,[16] 2005	776/3737 (20.8)	917/3724 (24.6)	0.80 (0.72-0.89)
SEARCH,[5] 2010	1184/5398 (21.9)	1214/5399 (22.5)	0.97 (0.88-1.06)
Pooled odds ratio	**3134/16 408 (19.1)**	**3550/16 344 (21.7)**	**0.84 (0.75-0.94)**
Heterogeneity: $I^2 = 74\%$; $P = .004$			



Data marker size indicates relative weight of the studies; OR, odds ratio; and CI, confidence interval.

JAMA 2011

AHA / ACC

Primary Prevention in Individuals With Diabetes Mellitus and LDL–C 70-189 mg/dL				
1. Moderate-intensity statin therapy should be initiated or continued for adults 40 to 75 years of age with diabetes mellitus.	A (Strong)	19, 29-34, 40	I	A
2. High-intensity statin therapy is reasonable for adults 40 to 75 years of age with diabetes mellitus with a ≥7.5% estimated 10-year ASCVD risk‖ unless contraindicated.	E (Expert Opinion)	---	IIa	B (49,52)
3. In adults with diabetes mellitus, who are <40 or >75 years of age, it is reasonable to evaluate the potential for ASCVD benefits and for adverse effects, for drug-drug interactions, and to consider patient preferences when deciding to initiate, continue, or intensify statin therapy.	E (Expert Opinion)	---	IIa	C (53-62)

Nobel Prizes and Laureates

Medicine Prizes ▾ 1985

▼About the Nobel Prize in Physiology or Medicine 1985
- Summary
- Press Release
- Award Ceremony Speech

▶ Michael S. Brown
▶ Joseph L. Goldstein

All Nobel Prizes in Physiology or Medicine
All Nobel Prizes in 1985

The Nobel Prize in Physiology or Medicine 1985
Michael S. Brown, Joseph L. Goldstein

The Nobel Prize in Physiology or Medicine 1985

Michael S. Brown

Joseph L. Goldstein

The Nobel Prize in Physiology or Medicine 1985 was awarded jointly to Michael S. Brown and Joseph L. Goldstein *"for their discoveries concerning the regulation of cholesterol metabolism"*

Photos: Copyright © The Nobel Foundation

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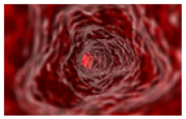
To cite this page
MLA style: "The Nobel Prize in Physiology or Medicine 1985". *Nobelprize.org*. Nobel Media AB 2013. Web. 28 Jan 2014.
<http://www.nobelprize.org/nobel_prizes/medicine/laureates/1985/>

Recommended:

Play the Blood Typing

Facts on the Nobel



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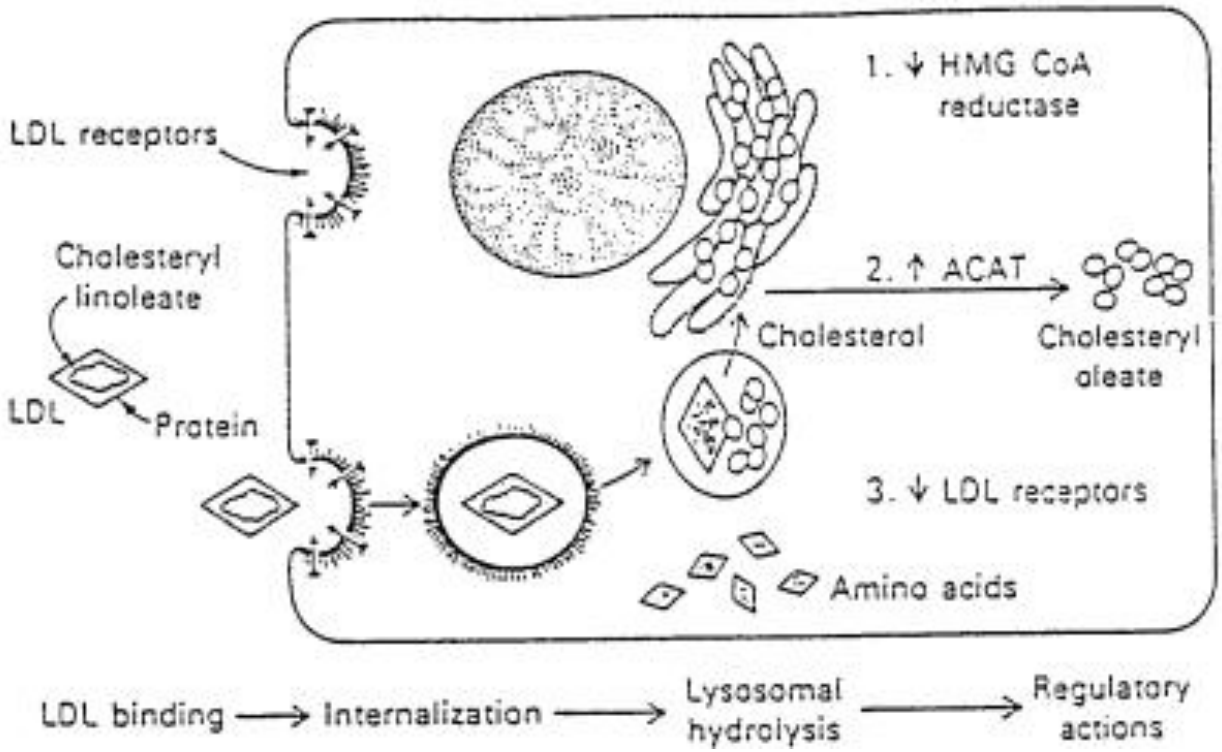

LDL receptors
Cholesteryl linoleate
LDL
Protein
1. ↓ HMG CoA reductase
2. ↑ ACAT
Cholesterol
Cholesteryl oleate
3. ↓ LDL receptors
Amino acids
LDL binding
Internalization
Lysosomal hydrolysis
Regulatory actions

THE JOURNAL OF BIOLOGICAL CHEMISTRY

Author(s):

Joseph L. Goldstein and Michael S. Brown

Title:

Binding and Degradation of Low Density Lipoproteins by Cultured Human Fibroblasts: Comparison of Cells from Normal Subjects and from Patients with Homozygous Familial Hypercholesterolemia

Comments:

This is a most interesting paper and I wish I could recommend its acceptance without reservations.....

Page 2 .....

Page 3 .....

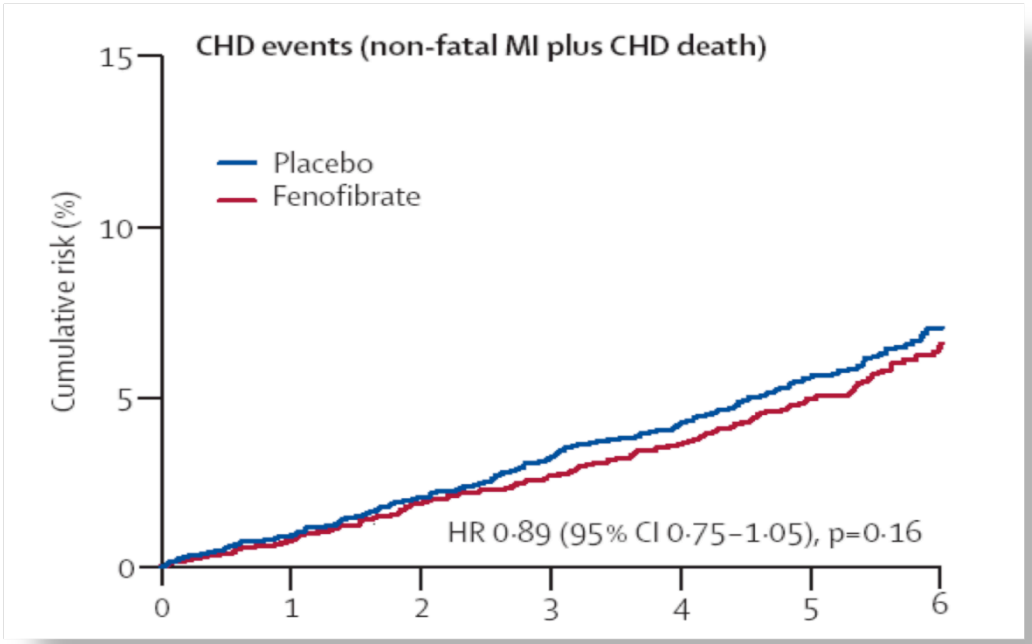
It is my considered opinion that publication of this paper with its incomplete observations would not serve medical science nor would it earn credit in the long run to its authors

Kresge N et al. J. Biol. Chem. 2006;281:e25

©2006 by American Society for Biochemistry and Molecular Biology

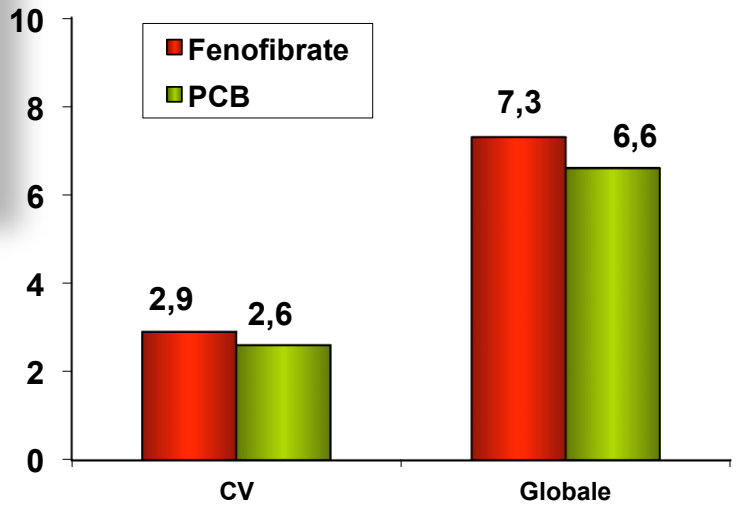
FIELD

(Fenofibrate Intervention and Event Lowering in Diabetes)



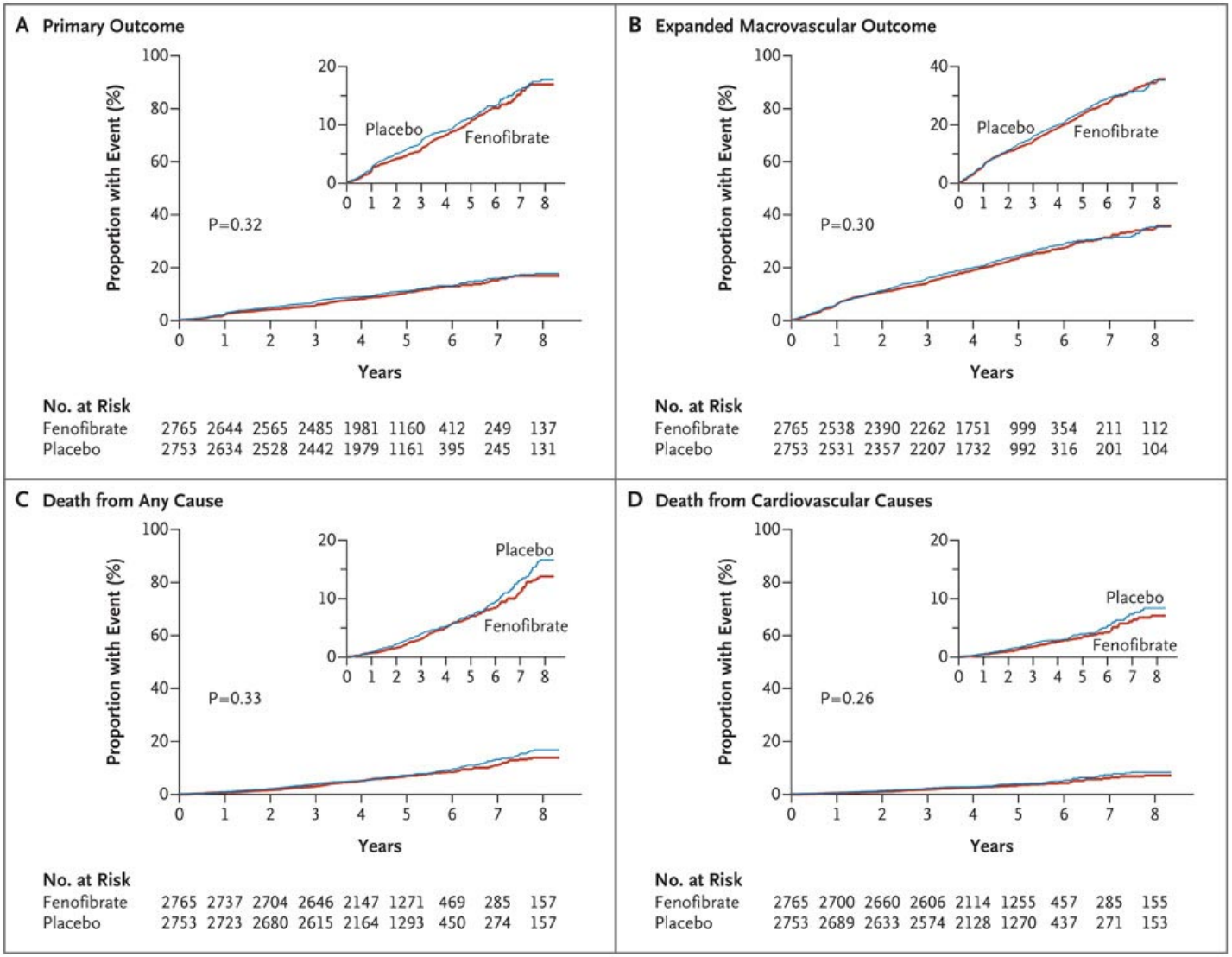
9 795 diabétiques type 2
50 à 75 ans en prévention I^{aire} et II^{aire}
cholestérol entre 1,16 et 2,51 g/L,
TG <4,43 g/L
Randomisation fenofibrate 200 mg vs PCB

Mortalité



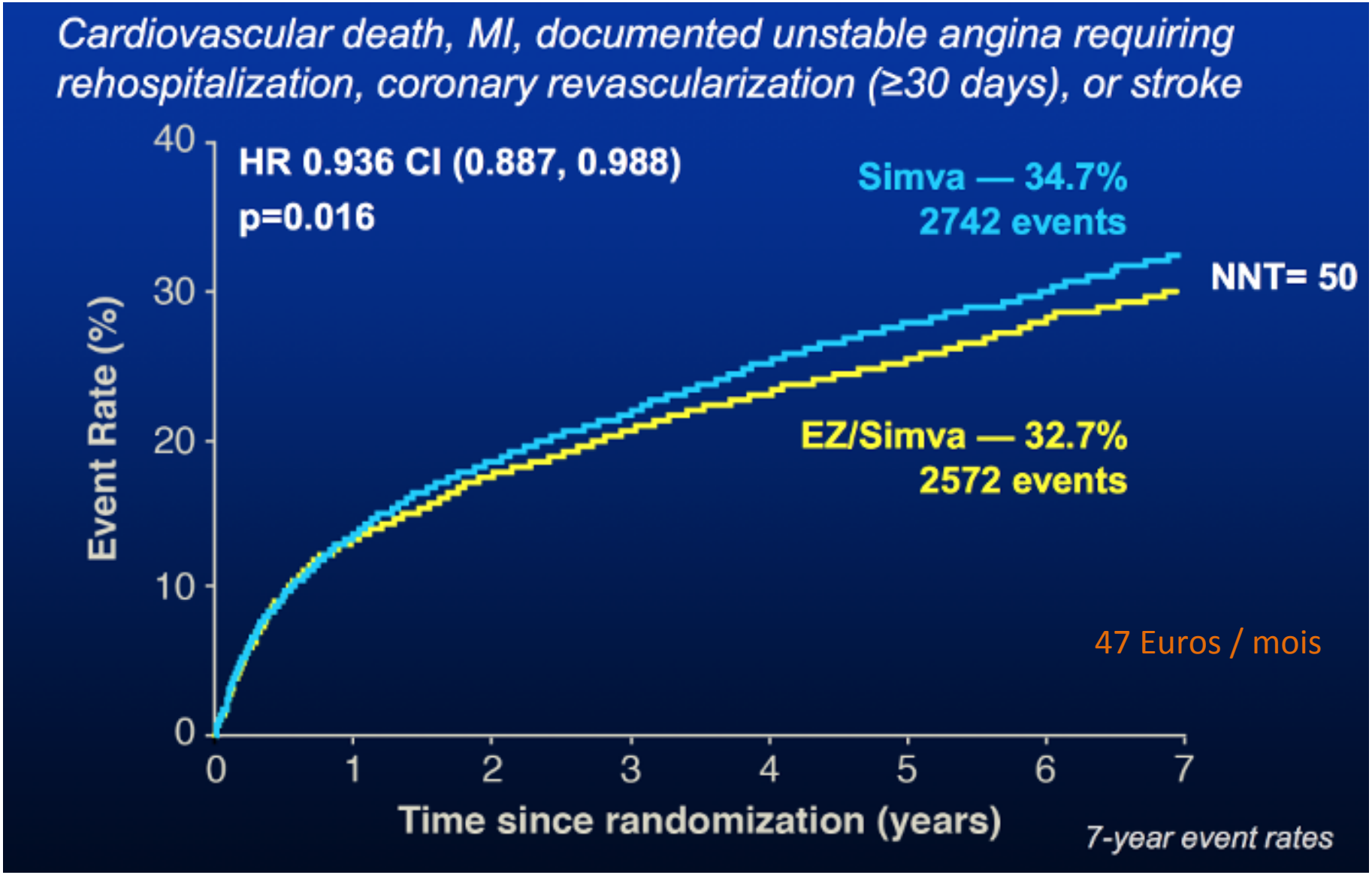
HR mortalité globale : 1.10 [0.95-1.29]

ACCORD Fenofibrate



The ACCORD Study Group. N Engl J Med 2010;10.1056/NEJMoa1001282

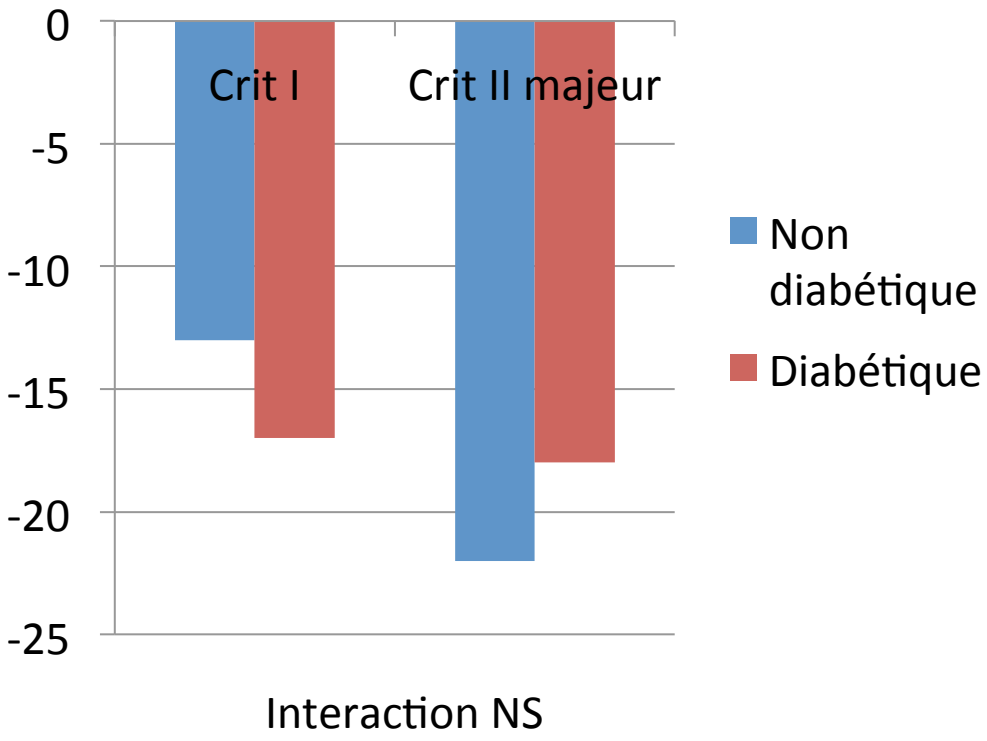
Ezetimibe


Cardiovascular death, MI, documented unstable angina requiring rehospitalization, coronary revascularization (≥30 days), or stroke
HR 0.936 CI (0.887, 0.988)
p=0.016
Simva — 34.7%
2742 events
NNT= 50
EZ/Simva — 32.7%
2572 events
47 Euros / mois
Event Rate (%)
40
30
20
10
0
0
1
2
3
4
5
6
7
Time since randomization (years)
7-year event rates

Fourier - diabétiques

500 - 700 Euros / mois

- 11031 patients avec diabète (40%)



Augmentation du nombre de diabètes

1,05 (0,94 – 1,17)

Sabatine et al Lancet Diabetes Endocrinol. 2017; (17)30313-3

Quelle est l'HbA1C optimale chez vos coronariens diabétiques ?

1. 9 – 10
2. 8 – 9
3. 7 – 8
4. 6,5 – 7
5. 6 – 6.5

Quelle est l'HbA1C optimale chez vos coronariens diabétiques ?

1. 9 – 10
2. 8 – 9
3. **7 – 8**
4. 6,5 – 7
5. 6 – 6.5

Double 2 X 2 Factorial Design

	BP		Lipid		
	Intensive (SBP<120)	Standard (SBP<140)	Statin + Masked Study Drug	Statin + Masked Study Drug	
Intensive Glycemia (A1C<6%)	1178	1193	1383	1374	5128*
Standard Glycemia (A1C 7-7.9%)	1184	1178	1370	1391	5123*
	2362*	2371*	2753*	2765*	10,251

**Primary analyses compare the marginals for main effects*

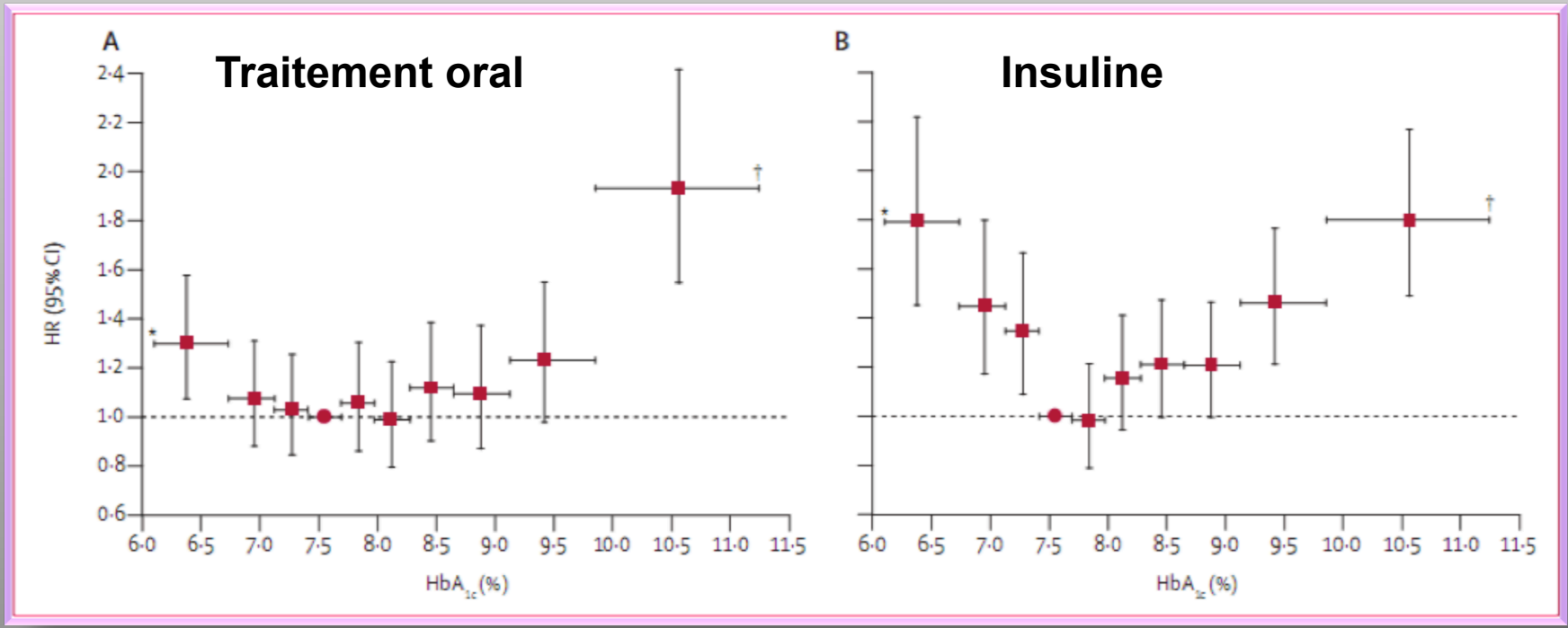
Buse, JB, et al, AmJCard 2007 99:21i-33i.

Primary & Secondary Outcomes

	Intensive N (%)	Standard N (%)	HR (95% CI)	P
Primary	352 (6.86)	371 (7.23)	0.90 (0.78-1.04)	0.16
Secondary				
Mortality	257 (5.01)	203 (3.96)	1.22 (1.01-1.46)	0.04
Nonfatal MI	186 (3.63)	235 (4.59)	0.76 (0.62-0.92)	0.004
Nonfatal Stroke	67 (1.31)	61 (1.19)	1.06 (0.75-1.50)	0.74
CVD Death	135 (2.63)	94 (1.83)	1.35 (1.04-1.76)	0.02
CHF	152 (2.96)	124 (2.42)	1.18 (0.93-1.49)	0.17

ACCORD Study Group, NEJM 2008 358:2545-2549.

Mortalité en fonction de HbA1c après intensification du traitement hypoglycémiant



- 47970 patients avec intensification du traitement hypoglycémiant
- Base de données des généralistes UK

Currie et al. Lancet 2010

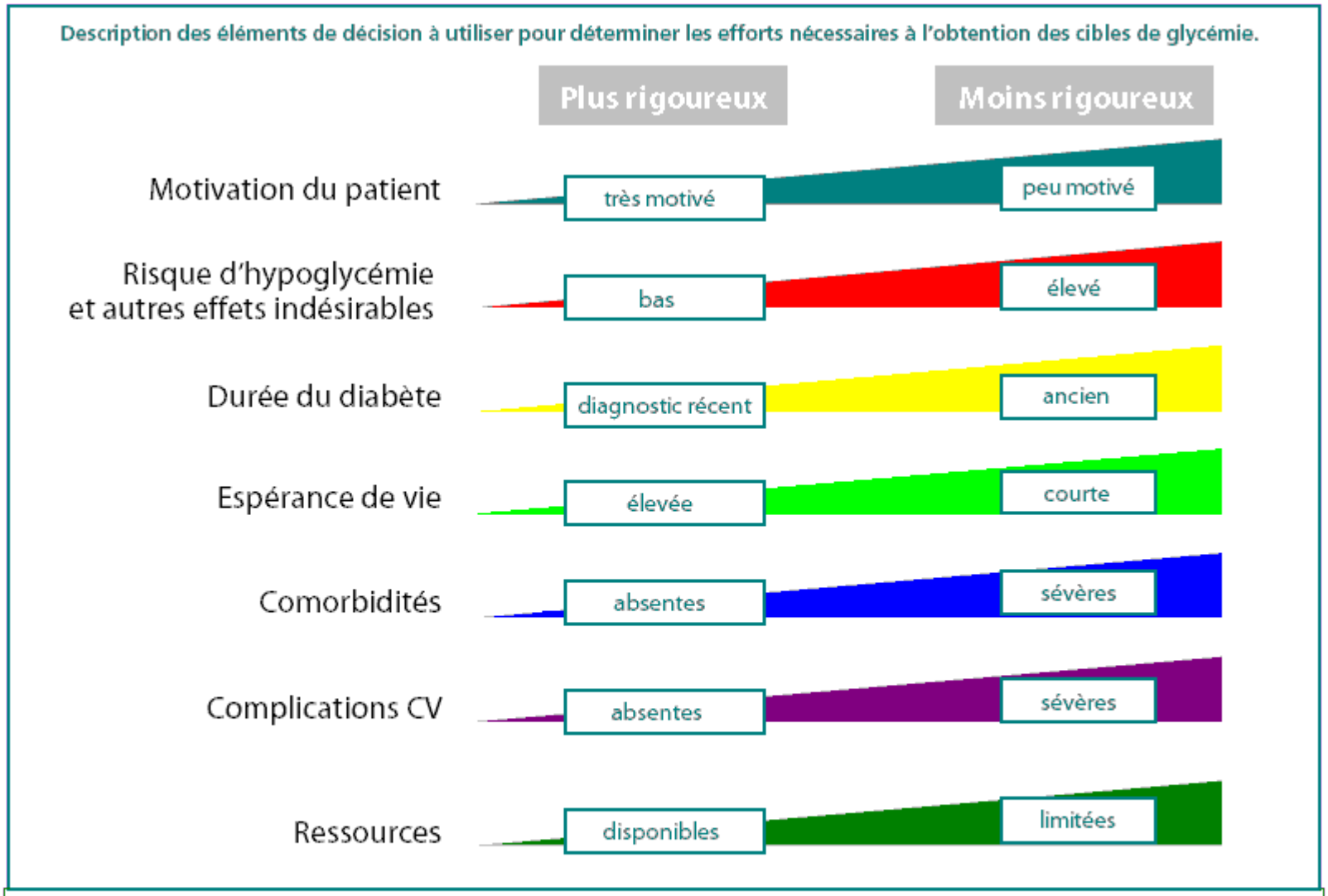


Figure 1. Description des éléments de décision à utiliser pour déterminer les efforts nécessaires à l'obtention des cibles de glycémie.

Le degré d'inquiétude dans un domaine particulier est représenté par la hauteur croissante de la rampe. Ainsi, lorsque des caractéristiques/des conjonctures particulières sont plus vers la gauche, des efforts plus marqués pour baisser l'HbA_{1c} sont justifiés, alors que, s'ils sont plus vers la droite, des efforts moins marqués sont acceptables. Si possible, de telles décisions doivent être prises en concertation avec le patient, en fonction de ses préférences, ses besoins et ses valeurs. Cette « échelle » n'a pas été conçue pour être appliquée de façon rigide mais comme une trame souple destinée à aider aux décisions cliniques. Adaptée avec la permission de Ismail-Beigi, et al [20].

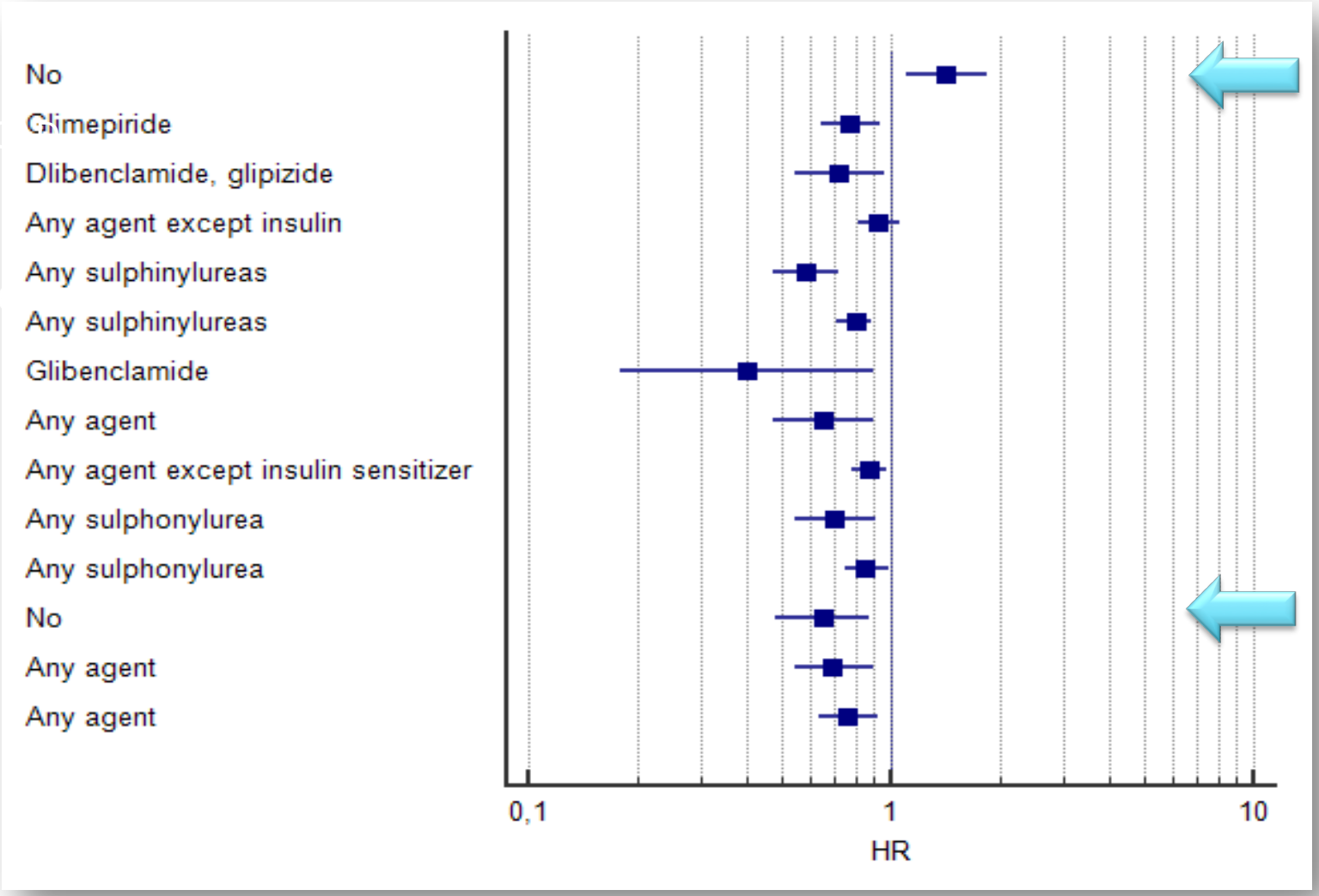
Traitement antidiabétique

- Quel traitement hypoglycémiant a montré une diminution des complications CV comparé à Placebo
  1. Metformine
  2. Sulfamides
  3. Glitazones
  4. DPP4
  5. GLP 1

Traitement antidiabétique

- Quel traitement hypoglycémiant a montré une diminution des complications CV comparé à Placebo
  1. Metformine
  2. Sulfamides
  3. Glitazones
  4. DPP4
  5. **GLP 1**

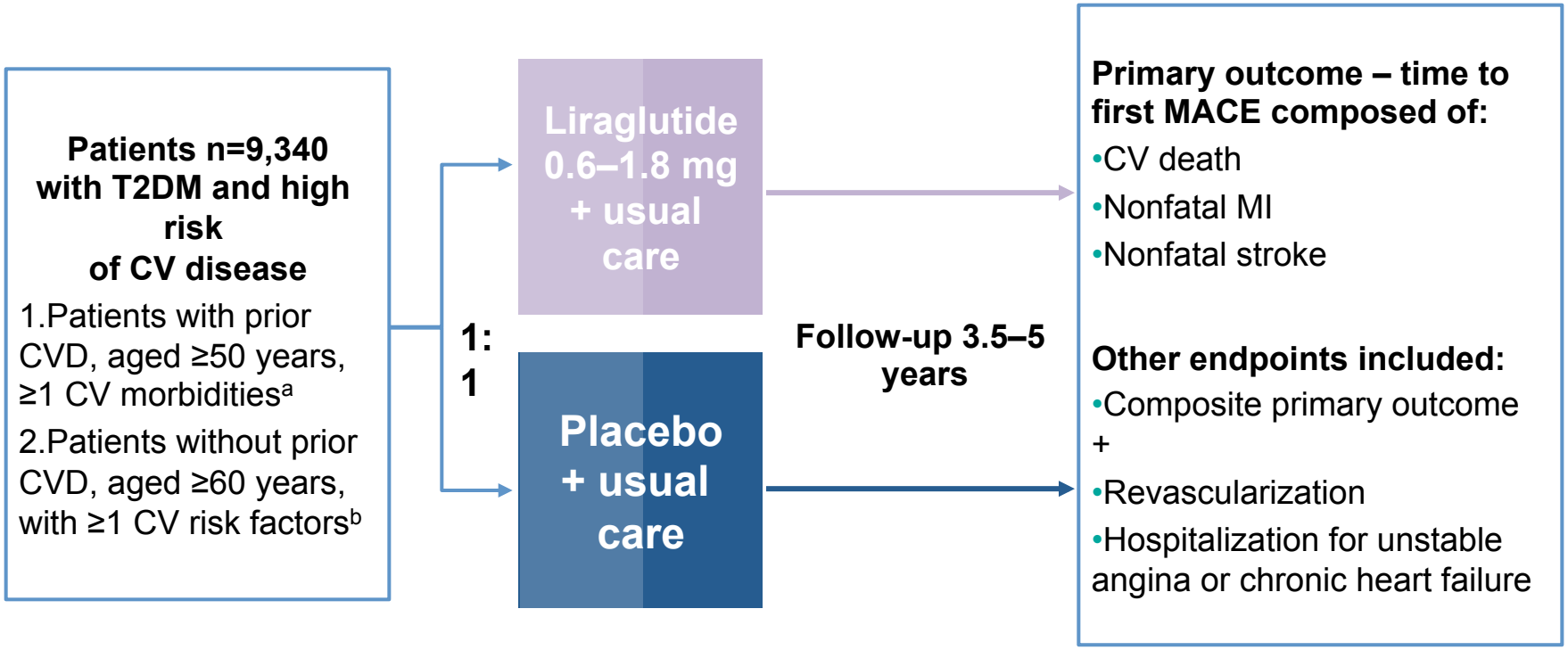
All causes mortality metformine



Fisman, 1999 – Schramm, 2011 – Pantalone, 2012 – Inzucchi, 2005 – Horsdal, 2008 – Jorgensen, 2010 – Melbin, 2011 – Masoudi, 2005 – Eurich, 2005 – Andersson 2010 – MacDonald, 2010 – Agular, 2011 – Roussel, 2010

LEADER Trial – Study Design

LEADER– Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results

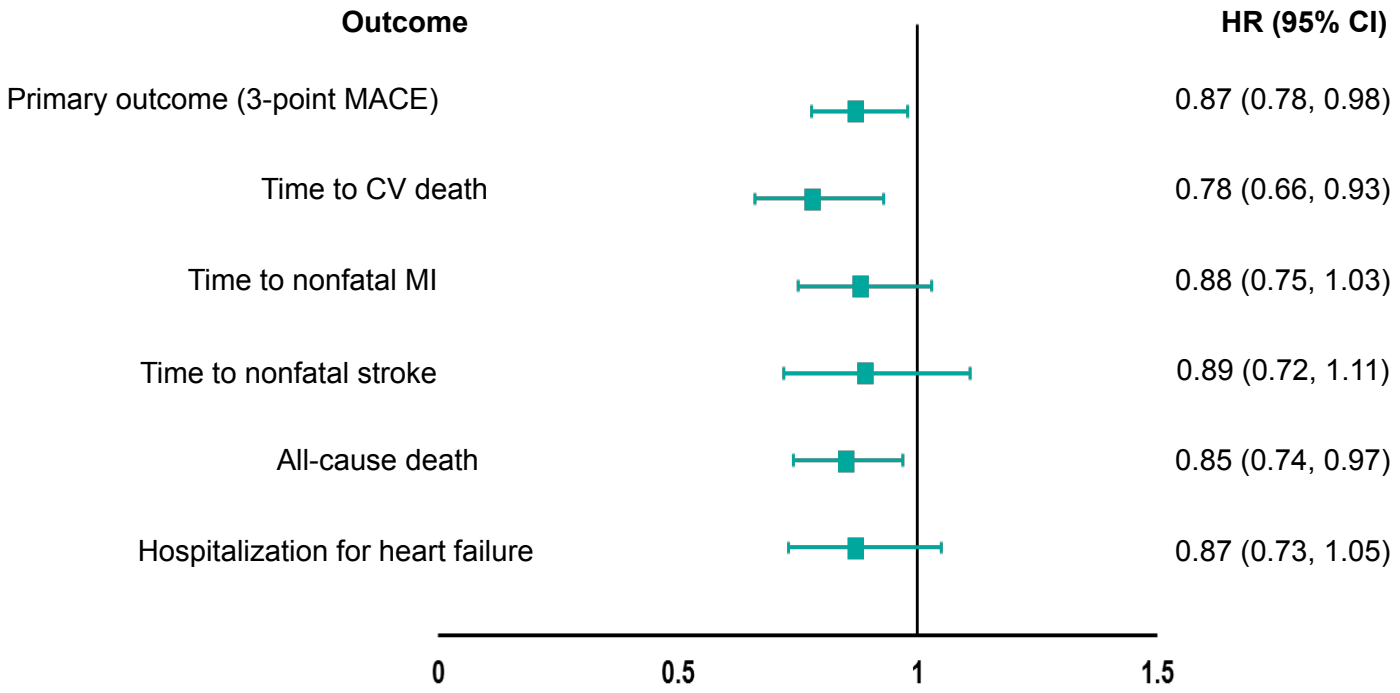


[a]Concomitant CVD, cerebrovascular disease, peripheral vascular disease, chronic renal failure, or chronic heart failure; [b]Microalbuminuria or proteinuria, hypertension, and left ventricular hypertrophy by ECG or imaging, left ventricular systolic or diastolic dysfunction by imaging; ankle–brachial index <0.9
CV, cardiovascular; CVD, cardiovascular disease; ECG, electrocardiogram; MI, myocardial infarction; SD, standard deviation; T2DM, Type 2 diabetes mellitus

Marso SP, et al. *Am Heart J* 2013;166:823–830

LEADER – Reduction of the Risk for 3-point MACE with Liraglutide Versus Placebo

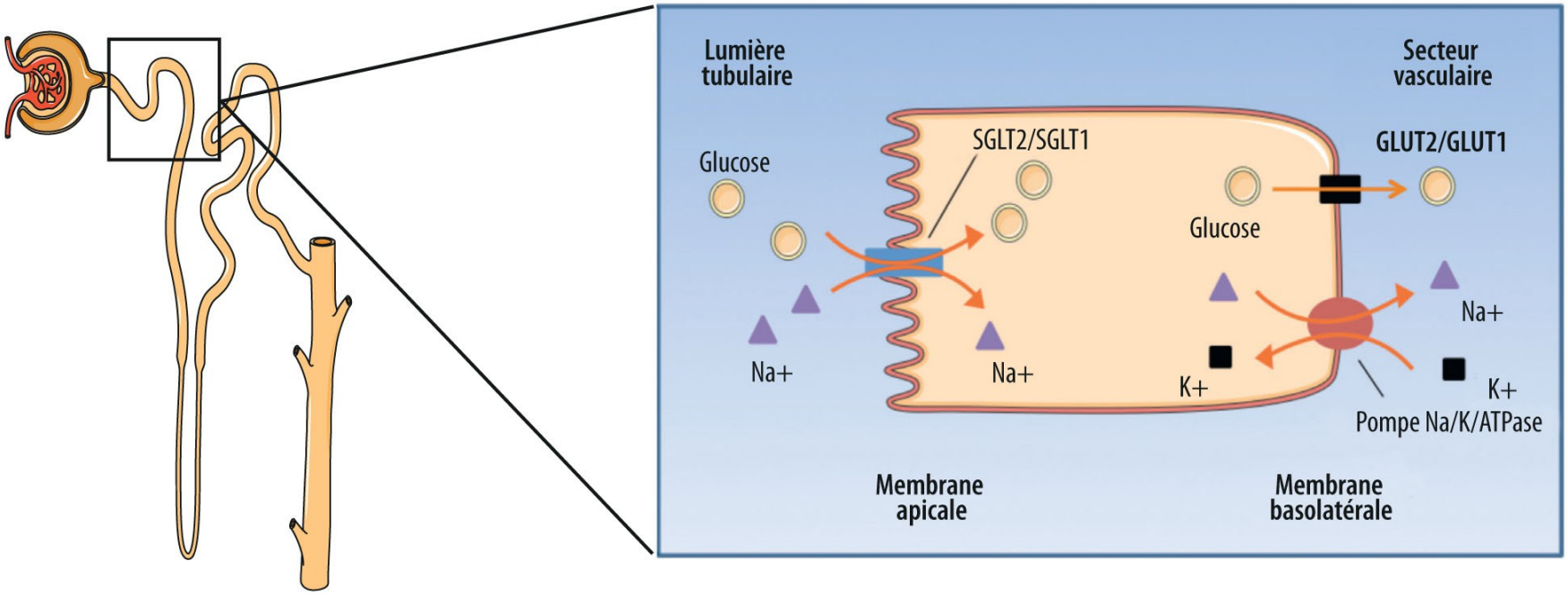
Hazard ratios for the primary endpoint, its components, and other endpoints



CI, confidence interval; CV, cardiovascular; LEADER, Liraglutide Effect and Action in Diabetes: Evaluation of cardiovascular outcome Results; MACE, major cardiovascular event; MI, myocardial infarction

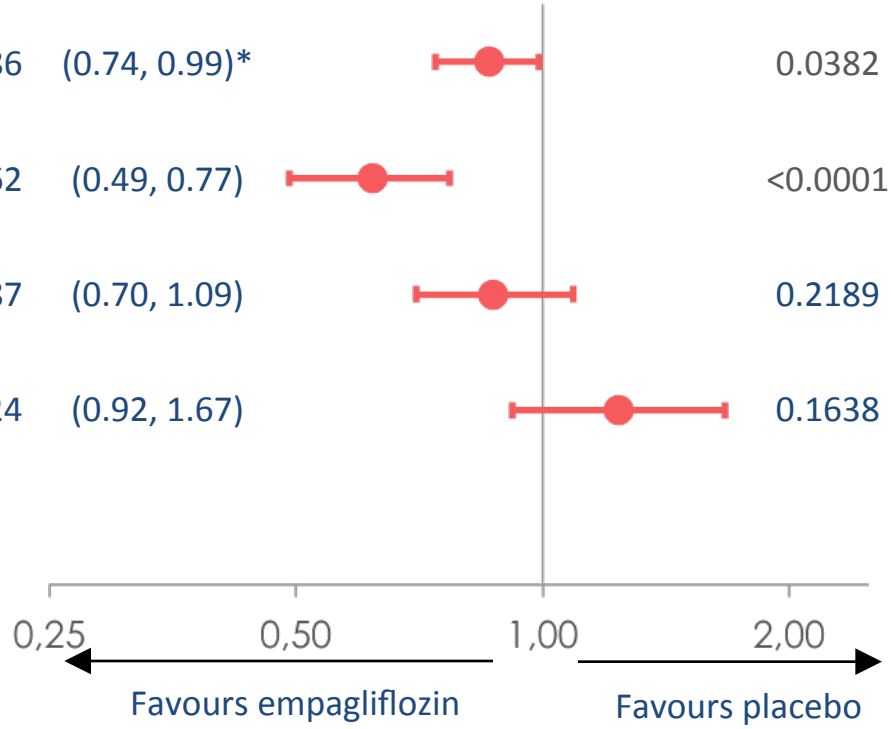
Marso S. Presented at the American Diabetes Association 76th Scientific Sessions, Session 3-CT-SY24. June 13 2016, New Orleans, LA, USA.

Inhibiteur SGLT2



Empareg outcome
CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction

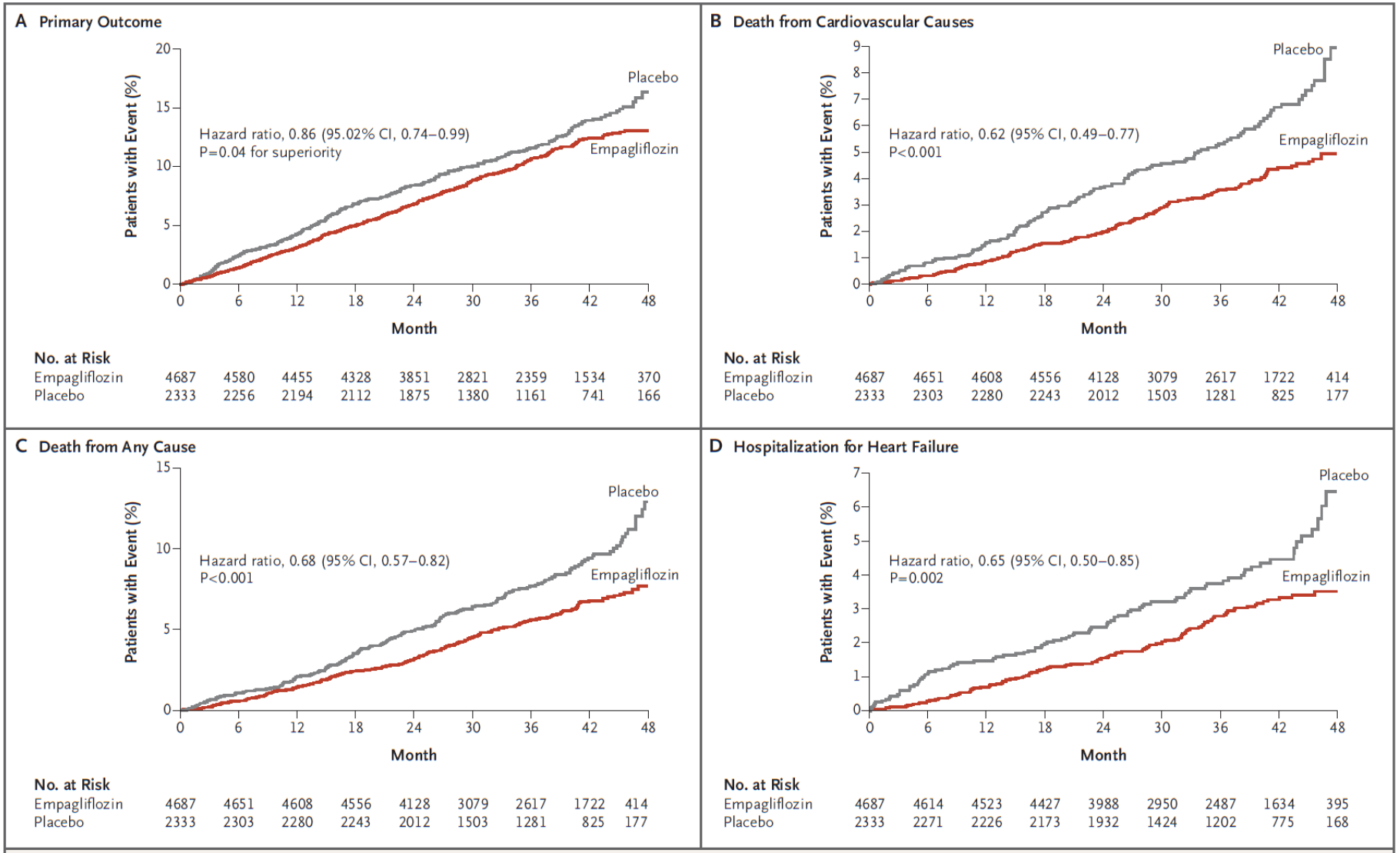


Figure 1. Cardiovascular Outcomes and Death from Any Cause.

Shown are the cumulative incidence of the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke) (Panel A), cumulative incidence of death from cardiovascular causes (Panel B), the Kaplan–Meier estimate for death from any cause (Panel C), and the cumulative incidence of hospitalization for heart failure (Panel D) in the pooled empagliflozin group and the placebo group among patients who received at least one dose of a study drug. Hazard ratios are based on Cox regression analyses.

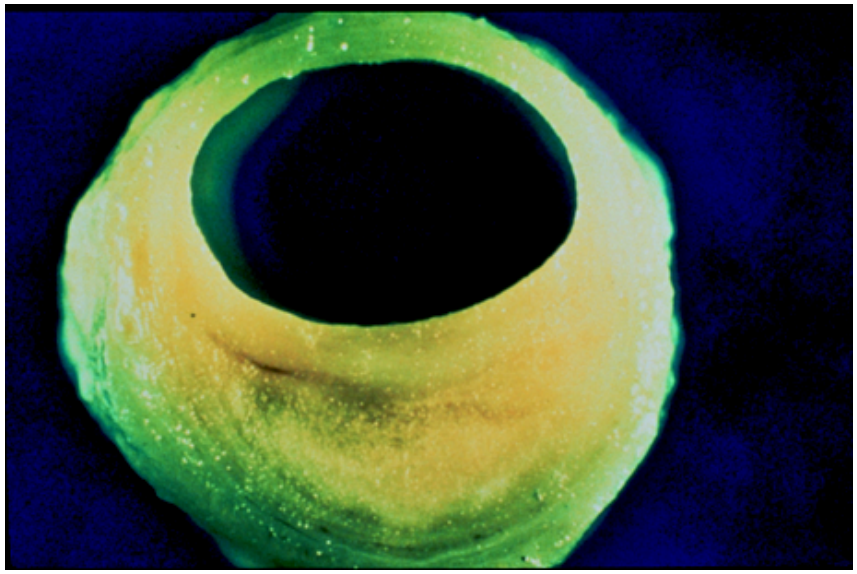
Empareg outcome, NEJM 2015

Revascularisation myocardique

Table 16 Specific recommendations for diabetic patients

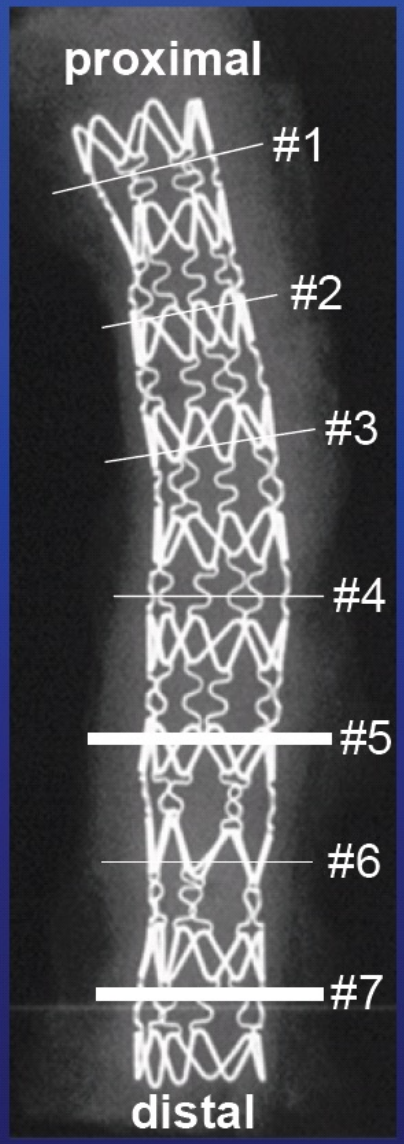
	Class[a]	Level[b]	Ref.[c]
In patients presenting with STEMI, primary PCI is preferred over fibrinolysis if it can be performed within recommended time limits.	I	A	112
In stable patients with extensive CAD, revascularization is indicated in order to improve MACCE-free survival.	I	A	111
Use of DES is recommended in order to reduce restenosis and repeat TVR.	I	A	115
In patients on metformin, renal function should be carefully monitored after coronary angiography/PCI.	I	C	—
CABG should be considered, rather than PCI, when the extent of the CAD justifies a surgical approach (especially MVD), and the patient's risk profile is acceptable.	IIa	B	29, 34, 113, 116
In patients with known renal failure undergoing PCI, metformin may be stopped 48 h before the procedure.	IIb	C	—
Systematic use of GIK in diabetic patients undergoing revascularization is not indicated.	III	B	117, 118, 122

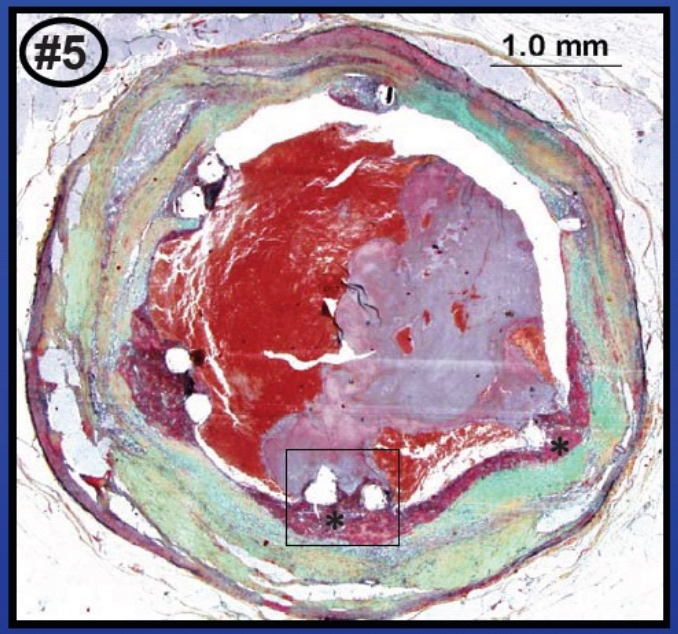
Facteur de risque de resténose

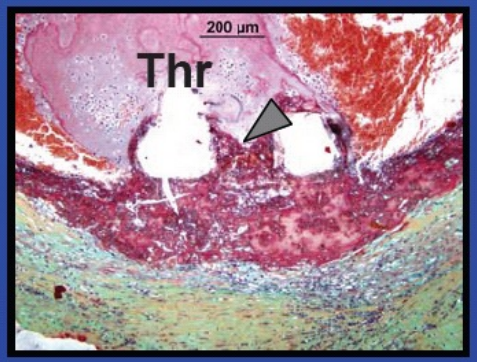


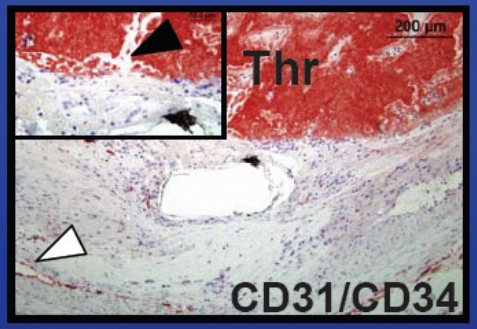
- Petit diamètre artériel
- Lésions longues
- Diabète

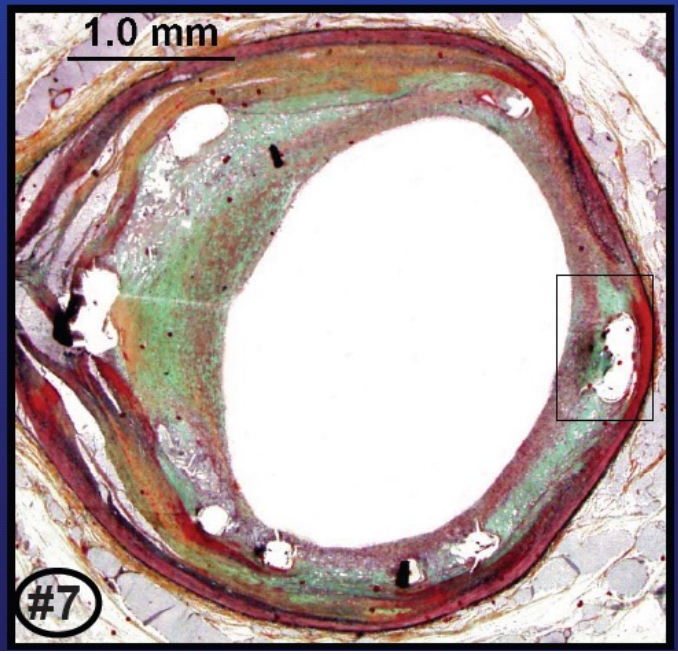
Lack of Re-Endothelialization at Sites of Thrombosis in DES

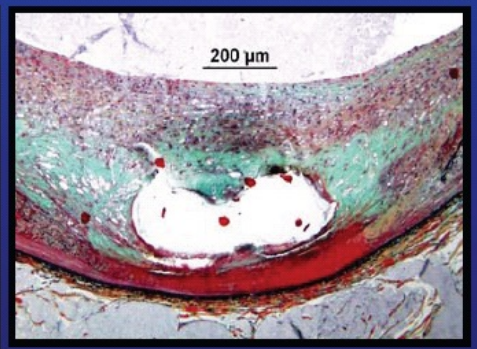


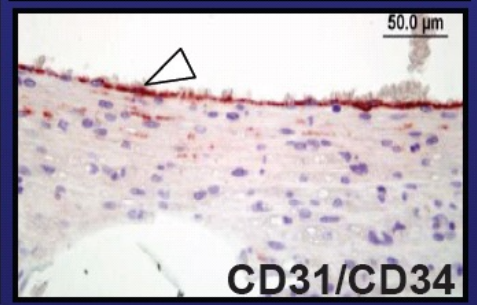












Risque de thrombose de stent chez les diabétiques

HR or OR
Diabetics
Multivariate

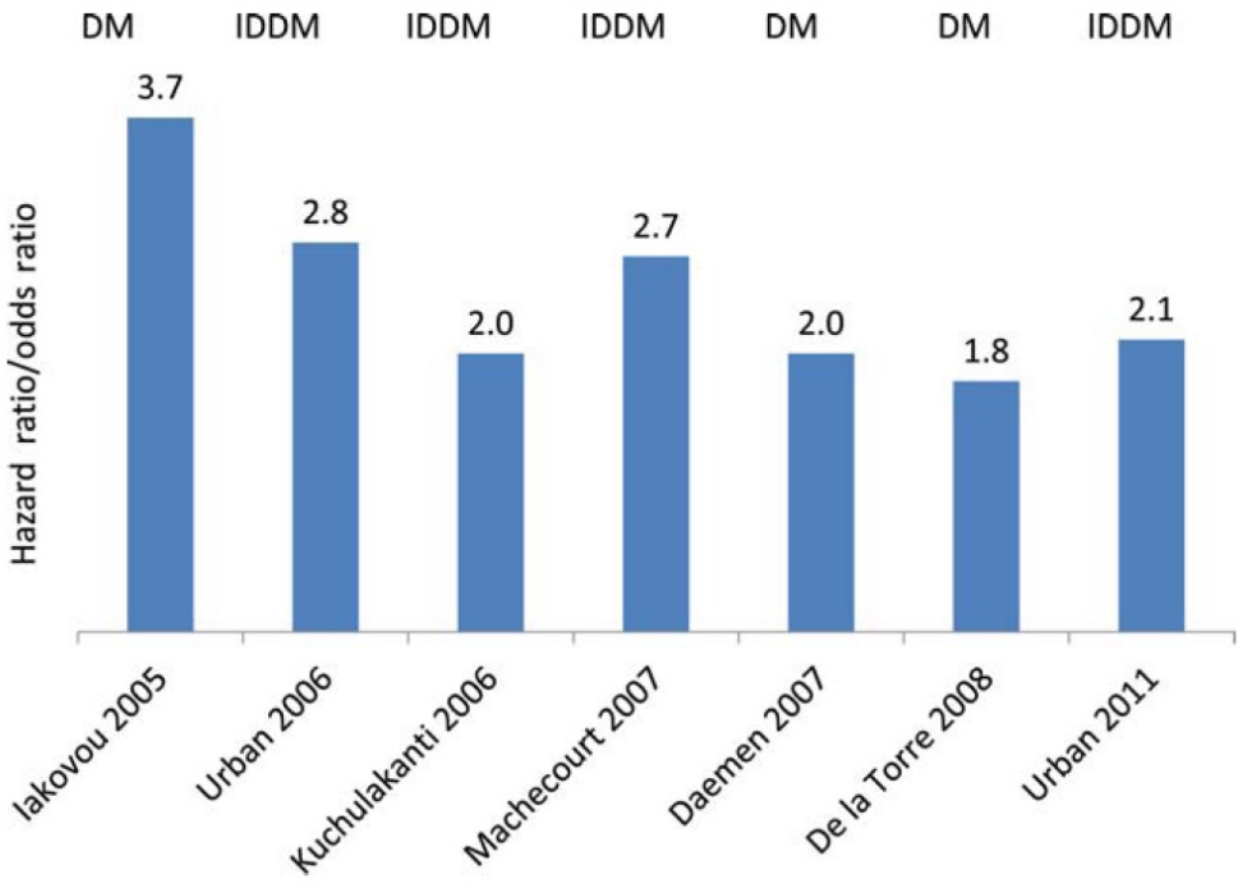


Table 16 Specific recommendations for diabetic patients

	Class[a]	Level[b]	Ref.[c]
In patients presenting with STEMI, primary PCI is preferred over fibrinolysis if it can be performed within recommended time limits.	I	A	112
In stable patients with extensive CAD, revascularization is indicated in order to improve MACCE-free survival.	I	A	111
Use of DES is recommended in order to reduce restenosis and repeat TVR.	I	A	115
In patients on metformin, renal function should be carefully monitored after coronary angiography/PCI.	I	C	—
CABG should be considered, rather than PCI, when the extent of the CAD justifies a surgical approach (especially MVD), and the patient's risk profile is acceptable.	IIa	B	29, 34, 113, 116
In patients with known renal failure undergoing PCI, metformin may be stopped 48 h before the procedure.	IIb	C	—
Systematic use of GIK in diabetic patients undergoing revascularization is not indicated.	III	B	117, 118, 122

Angioplastie ou Pontage ?

FREEDOM Design (1)

Eligibility: DM patients with MV-CAD eligible for stent or surgery
Exclude: Patients with acute STEMI

Randomized 1:1

MV-Stenting
With Drug-eluting

CABG
With or Without CPB

All concomitant Meds shown to be beneficial were encouraged,
including: clopidogrel, ACE inhib., ARBs, b-blockers, statins

TRIAL SCREENING & ENROLLMENT

32,966 Patients were screened for eligibility

3,309 were eligible (10%)

1,409 did not consent

1,900 consented (57%)

953 Randomized to PCI/DES*

5 underwent CABG
3 withdrew prior to procedure
3 died prior to procedure
3 underwent neither PCI/DES or CABG

16 withdrew post-procedure

43 were lost to follow-up

947 Randomized to CABG

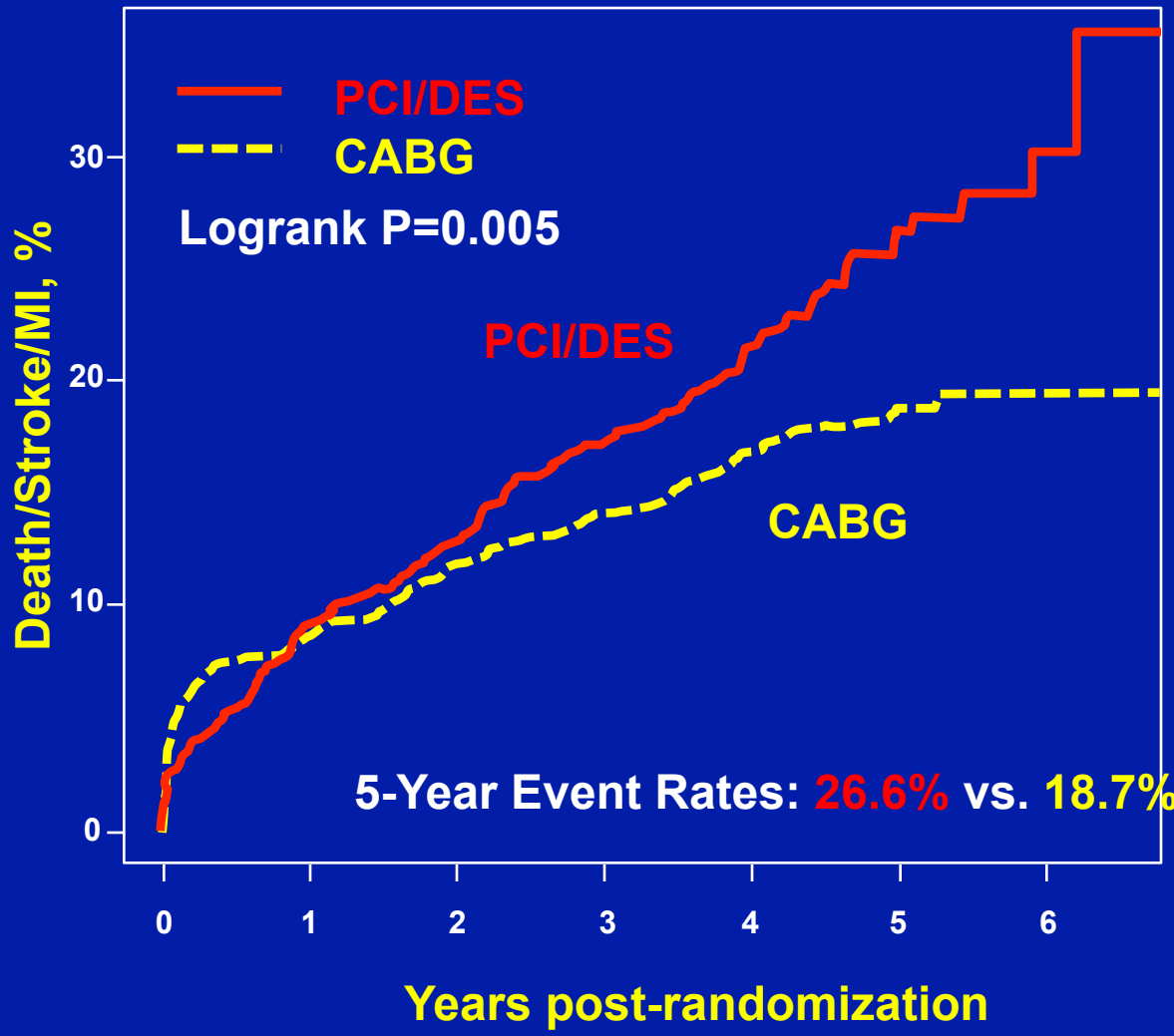
18 underwent PCI/DES
26 withdrew prior to procedure
3 died prior to procedure
7 underwent neither PCI/DES or CABG

36 withdrew post-procedure

51 were lost to follow-up

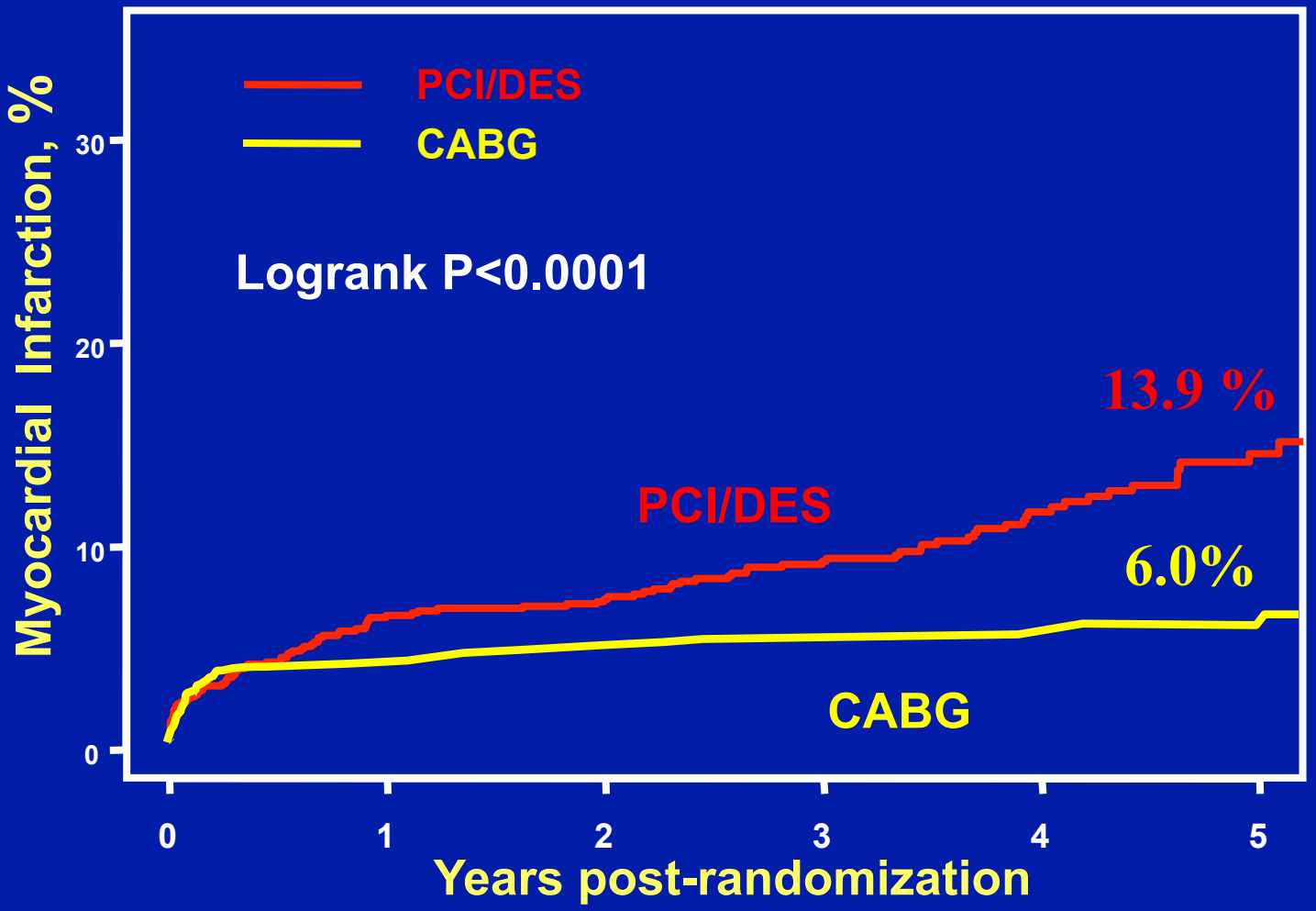
*953 and 947 included ITT analysis using all available follow-up time post-randomization

PRIMARY OUTCOME – DEATH / STROKE / MI



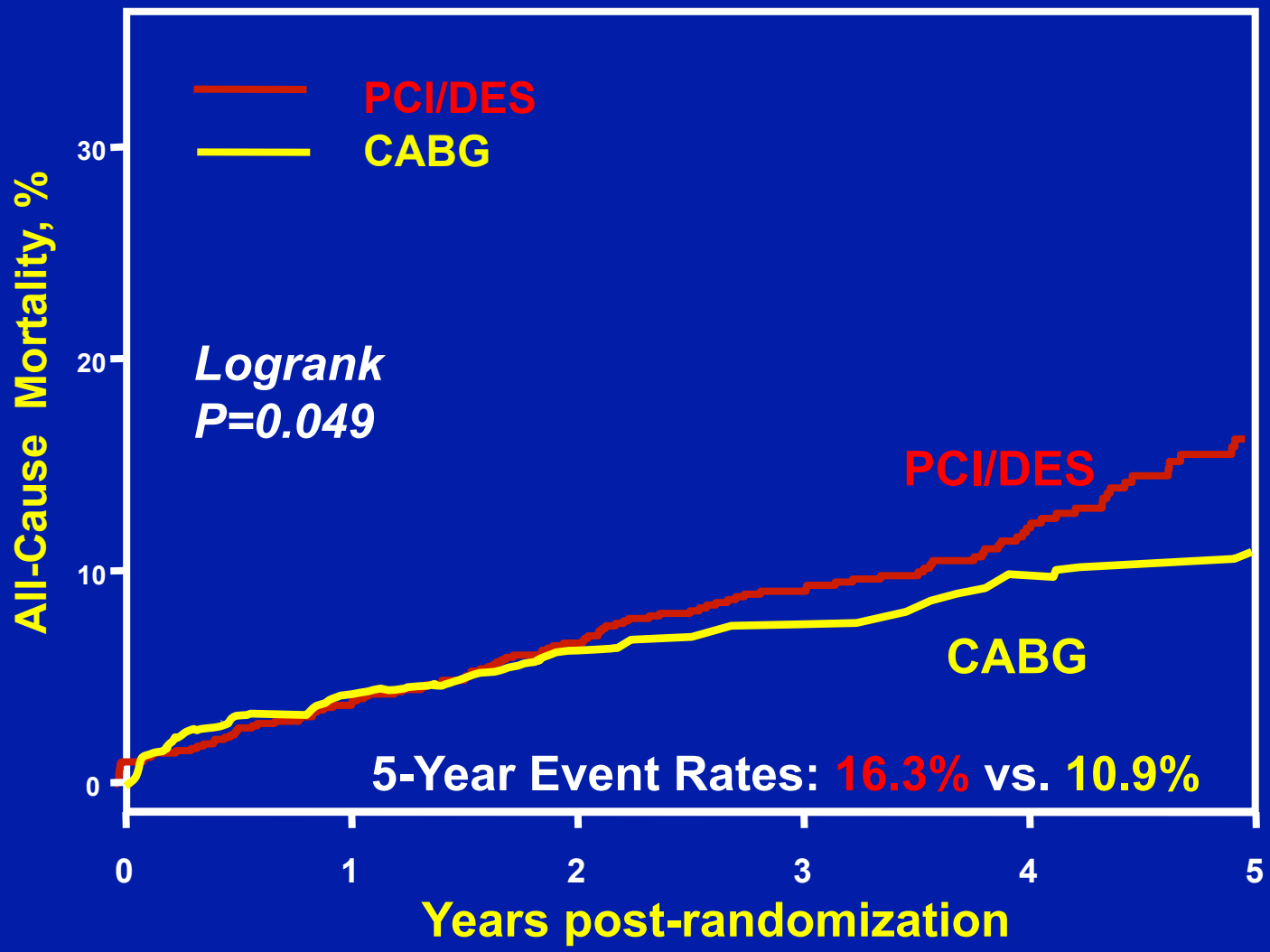
PCI/DES N	953	848	788	625	416	219	40
CABG N s	943	814	758	613	422	221	44

MYOCARDIAL INFARCTION



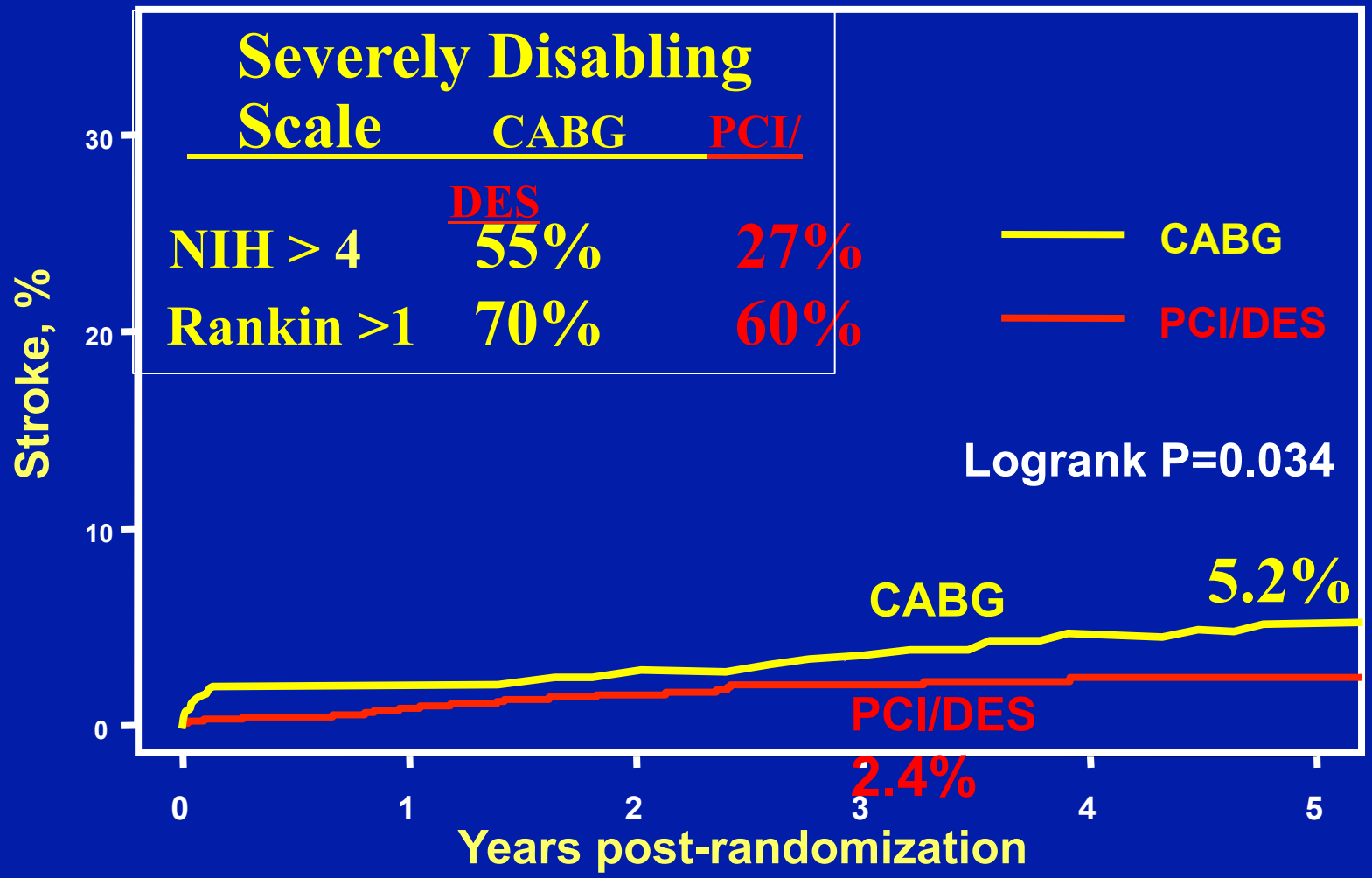
PCI/DES N 953	853	798	636	422	220
CABG N 947	824	772	629	432	229

ALL-CAUSE MORTALITY



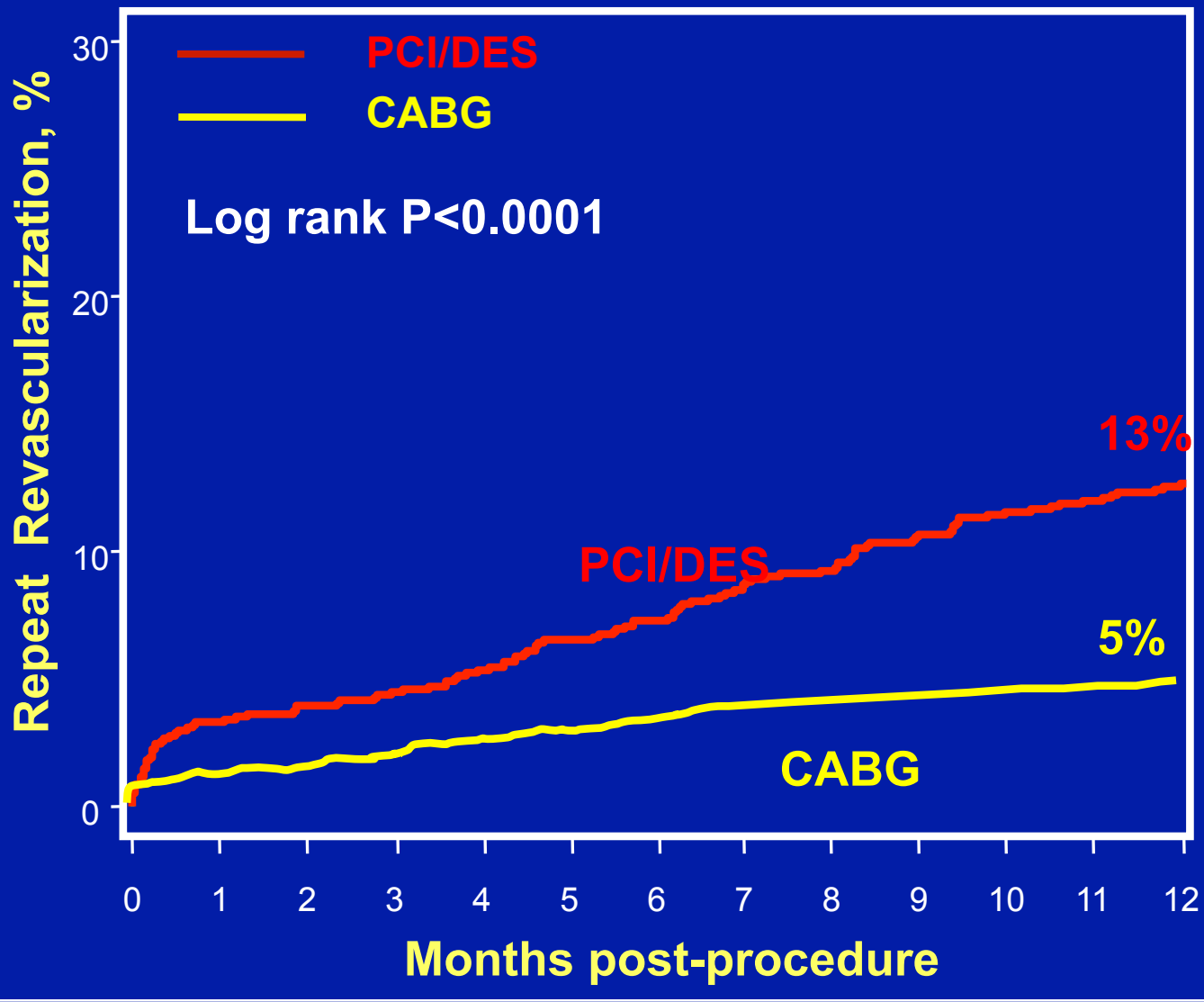
PCI/DES N	953	897	845	685	466	243
CABG N	947	855	806	655	449	238

STROKE

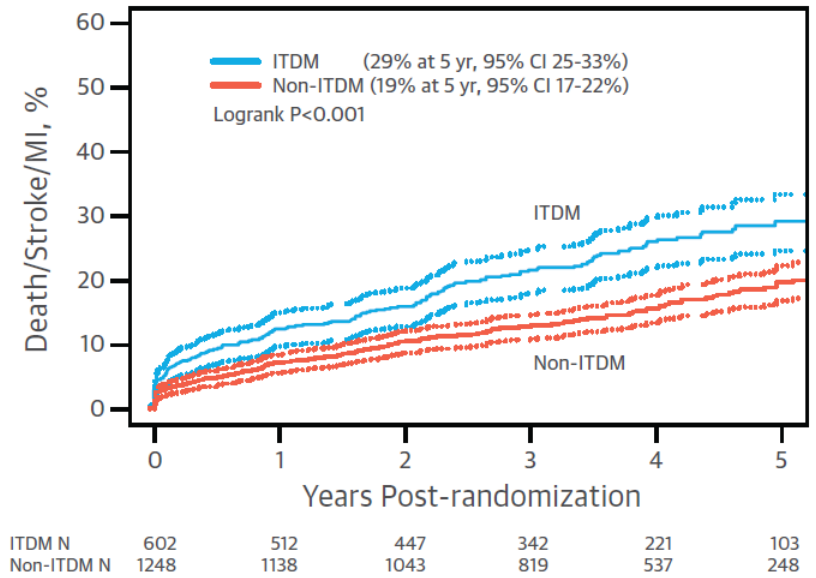


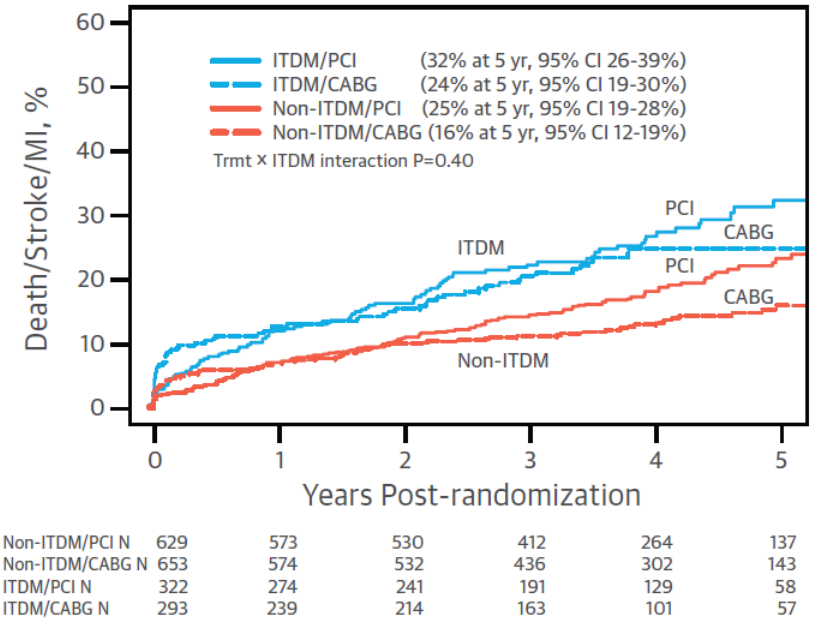
PCI/DES N	953	891	833	673	460	241
CABG N	947	844	791	640	439	230

REPEAT REVASCULARIZATION



PCI/DES №944	887	856	818	792
CABG №911	858	836	825	806





CENTRAL ILLUSTRATION Estimates of the Primary Endpoint by Treatment Received and Insulin Use

FREEDOM
Insulin / non insulin

TABLE 7 PCI Versus CABG Hazard Ratios for FREEDOM Primary Outcome of All-Cause Death/Stroke/MI: Time-Dependent Cox Regression Modeling Results*

Group	<2 Yrs Post-Procedure		≥2 Yrs Post-Procedure	
	Hazard Ratio (95% CI)	p Value	Hazard Ratio (95% CI)	p Value
All (n = 1,850)	1.11 (0.85-1.45)	0.44	2.06 (1.41-3.02)	<0.001
ITDM (n = 602)	1.06 (0.70-1,61)	0.78	1.52 (0.86-2.70)	0.15
Non-ITDM (n = 1,248)	1.12 (0.79-1.58)	0.54	2.46 (1.48-4.09)	<0.001

*Treatment group × time period interaction p values = 0.009 for all, 0.32 for ITDM, 0.012 for non-ITDM.

Abbreviations as in Tables 1 and 3.

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Surgical Versus Percutaneous Coronary Revascularization in Patients With Diabetes and Acute Coronary Syndromes

Krishnan Ramanathan, MB, ChB,[a] James G. Abel, MD,[a] Julie E. Park, MMath,[b] Anthony Fung, MBBS,[a] Verghese Mathew, MD,[c] Carolyn M. Taylor, MD,[a] G.B. John Mancini, MD,[a] Min Gao, MD, PhD,[b] Lillian Ding, MSc,[d] Subodh Verma, MD, PhD,[e] Karin H. Humphries, DSc,[a,b] Michael E. Farkouh, MD, MSc[f]

ABSTRACT

BACKGROUND Randomized trial data support the superiority of coronary artery bypass grafting (CABG) surgery over percutaneous coronary intervention (PCI) in diabetic patients with multivessel coronary artery disease (MV-CAD). However, whether this benefit is seen in a real-world population among subjects with stable ischemic heart disease (SIHD) and acute coronary syndromes (ACS) is unknown.

OBJECTIVES The main objective of this study was to assess the generalizability of the FREEDOM (Future REvascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multi-vessel Disease) trial in real-world practice among patients with diabetes mellitus and MV-CAD in residents of British Columbia, Canada. Additionally, the study evaluated the impact of mode of revascularization (CABG vs. PCI with drug-eluting stents) in diabetic patients with ACS and MV-CAD.

METHODS In a large population-based database from British Columbia, this study evaluated major cardiovascular outcomes in all diabetic patients who underwent coronary revascularization between 2007 and 2014 (n = 4,661, 2,947 patients with ACS). The primary endpoint (major adverse cardiac or cerebrovascular events [MACCE]) was a composite of all-cause death, nonfatal myocardial infarction, and nonfatal stroke. The risk of MACCE with CABG or PCI was compared using multivariable adjustment and a propensity score model.

RESULTS At 30-days post-revascularization, for ACS patients the odds ratio for MACCE favored CABG 0.49 (95% confidence interval [CI]: 0.34 to 0.71), whereas among SIHD patients MACCE was not affected by revascularization strategy (odds ratio: 1.46; 95% CI: 0.71 to 3.01; $p_{interaction} < 0.01$). With a median follow-up of 3.3 years, the late (31-day to 5-year) benefit of CABG over PCI no longer varied by acuity of presentation, with a hazard ratio for MACCE in ACS patients of 0.67 (95% CI: 0.55 to 0.81) and the hazard ratio for SIHD patients of 0.55 (95% CI: 0.40 to 0.74; $p_{interaction} = 0.28$).

CONCLUSIONS In diabetic patients with MV-CAD, CABG was associated with a lower rate of long-term MACCE relative to PCI for both ACS and SIHD. A well-powered randomized trial of CABG versus PCI in the ACS population is warranted because these patients have been largely excluded from prior trials. (J Am Coll Cardiol 2017;70:2995-3006)
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TABLE 1 Baseline Characteristics by Mode of Revascularization (PCI vs. CABG)

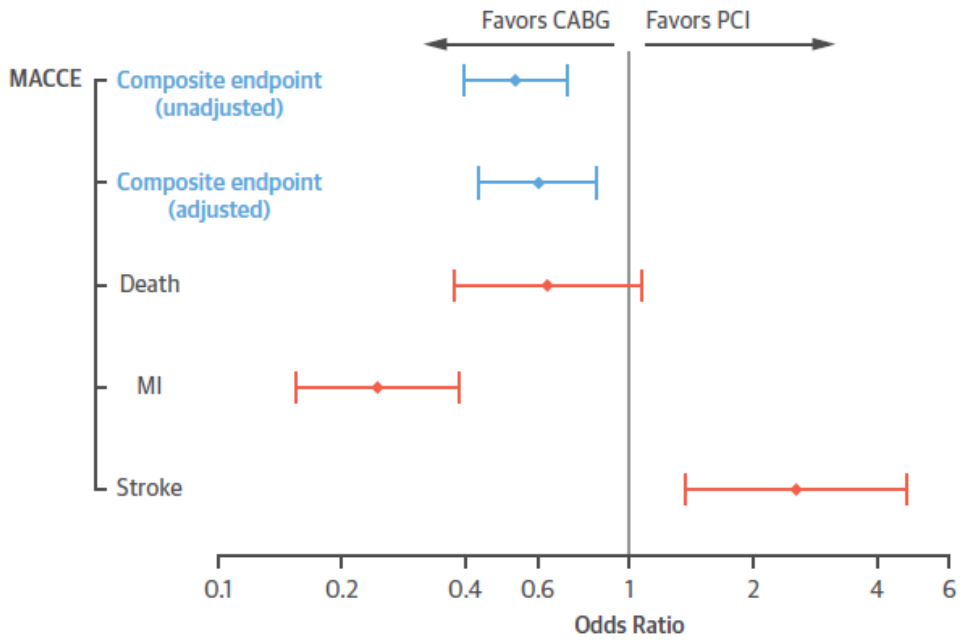
	PCI (n = 2,888)	CABG (n = 1,931)	p Value
Age, yrs	67.3 ± 10.8	65.2 ± 9.0	<0.01
Female	810 (28.0)	441 (22.8)	<0.01
Hyperlipidemia	2,237 (77.5)	1,538 (79.6)	0.07
Hypertension	2,545 (88.1)	1,772 (91.8)	<0.01
Peripheral arterial disease	409 (14.2)	235 (12.2)	0.05
Pulmonary disease	476 (16.5)	231 (12.0)	<0.01
Renal insufficiency*	204 (7.1)	133 (6.9)	0.81
Liver gastrointestinal disease	421 (14.6)	216 (11.2)	<0.01
Malignant disease	282 (9.8)	153 (7.9)	0.03
3-vessel disease	815 (28.2)	1,241 (64.3)	<0.01
LAD			<0.01
Proximal	683 (23.6)	868 (45.0)	
Other LAD	1,589 (55.0)	971 (50.3)	
Type 2 DM	2,840 (98.3)	1,878 (97.3)	0.01
ACS (vs. SIHD)	1,966 (68.1)	1,051 (54.4)	<0.01
CCS (III or IV)	2,075 (71.8)	1,196 (61.9)	<0.01
Urgency			<0.01
Elective	864 (29.9)	794 (41.1)	
Urgent	1,923 (66.6)	1,079 (55.9)	
Emergency	100 (3.5)	58 (3.0)	
Ejection fraction			<0.01
>50%	1,579 (56.9)	1,269 (66.1)	
30%-50%	550 (19.8)	507 (26.4)	
<30%	132 (4.8)	86 (4.5)	
Not entered†	514 (18.5)	58 (3)	

Values are mean ± SD or n (%). *Dialysis or creatinine level >200 μmol/l. †Ejection fraction purposely not entered; combined with <30% group in adjusted models.

ACS = acute coronary syndrome; CABG = coronary artery bypass grafting; CCS = Canadian Cardiovascular Society angina scale; DM = diabetes mellitus; LAD = left anterior descending coronary artery; PCI = percutaneous coronary intervention; SIHD = stable ischemic heart disease.

Ramanathan K, JACC 2017; 70: 2995-3006

FIGURE 2 Plot of ORs (95% Confidence Intervals) for 30-Day (Early) Outcomes (CABG vs. PCI)



The early impact of revascularization modality on the primary outcome (major adverse cardiac or cerebrovascular event(s) [MACCE]), which was a composite of all-cause death, nonfatal myocardial infarction (MI), and nonfatal stroke, and secondary outcomes (the individual components of major adverse cardiac or cerebrovascular events) expressed as odds ratios (ORs). The odds ratios for primary outcome of MACCE was adjusted for age, sex, presentation (ACS vs. SIHD), urgency (emergent, urgent vs. elective) and LVEF (>50%, 30–50% vs. <30%). The X axis is on logarithmic scale. The odds ratios for each of the component outcomes favored coronary artery bypass grafting (CABG), except for stroke. The patients who underwent coronary artery bypass grafting had significantly lower odds of major adverse cardiac or cerebrovascular events and nonfatal myocardial infarction, compared with patients who underwent percutaneous coronary intervention (PCI).

Ramanathan K, JACC 2017; 70: 2995-3006

Table 16 Specific recommendations for diabetic patients

	Class[a]	Level[b]	Ref.[c]
In patients presenting with STEMI, primary PCI is preferred over fibrinolysis if it can be performed within recommended time limits.	I	A	112
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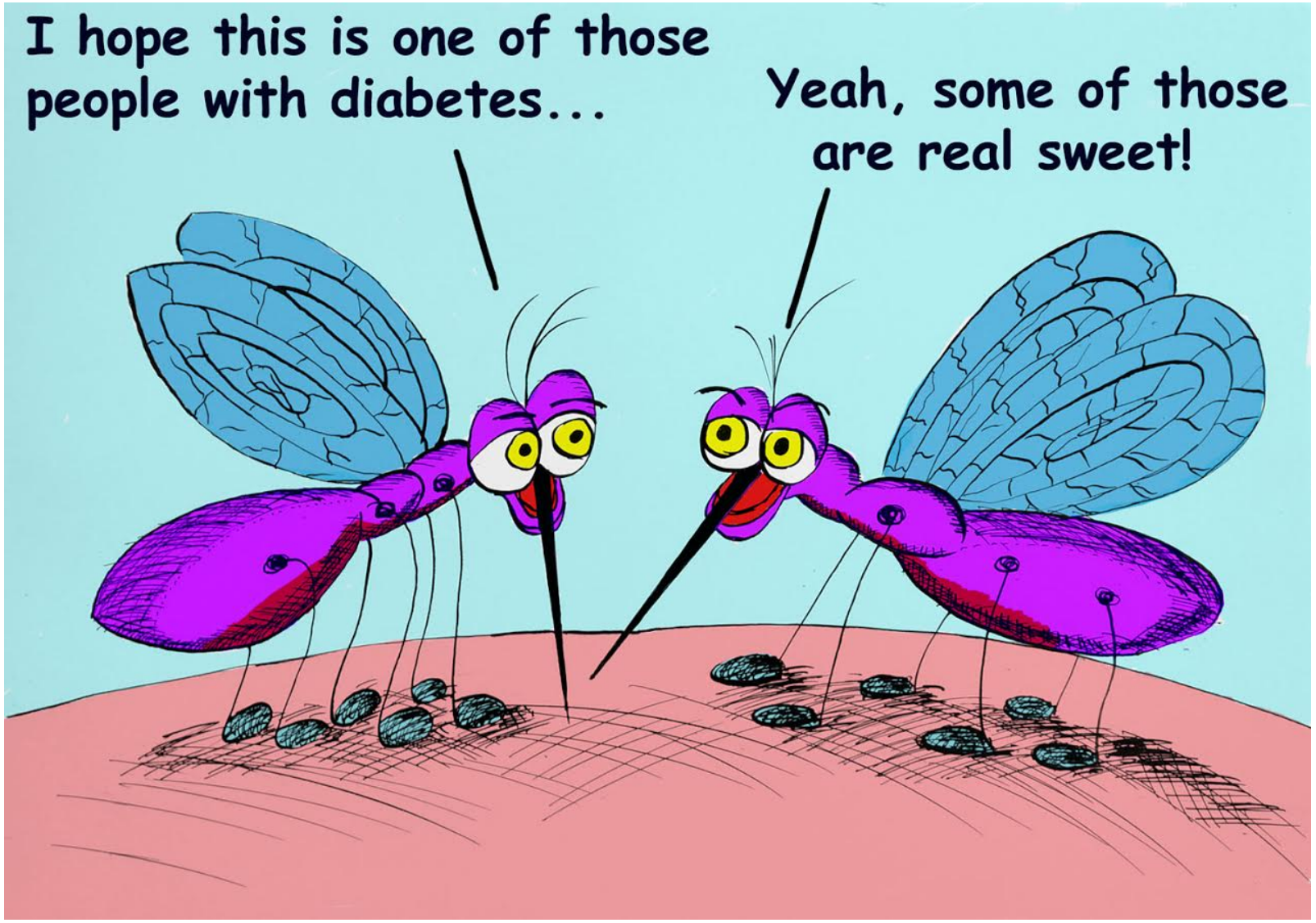
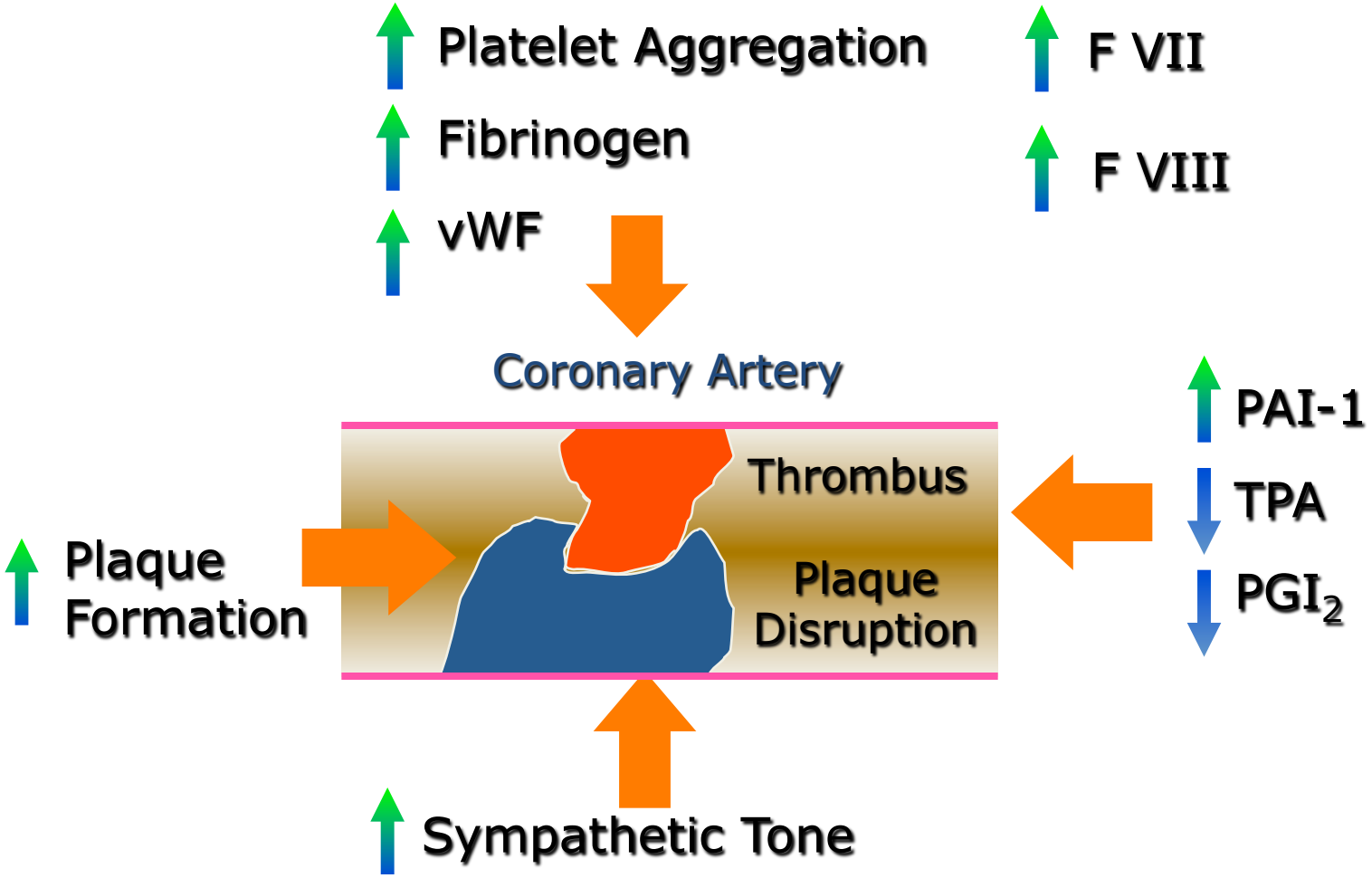
In patients with known renal failure undergoing PCI, metformin may be stopped 48 h before the procedure.	IIb	C	—
Systematic use of GIK in diabetic patients undergoing revascularization is not indicated.	III	B	117, 118, 122

Antiplatelet and anticoagulant treatment


I hope this is one of those people with diabetes...
Yeah, some of those are real sweet!

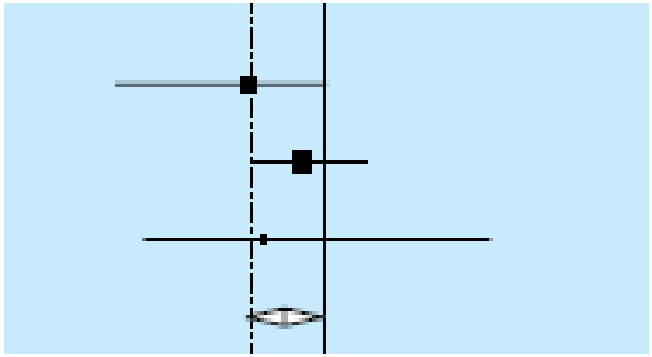
Diabetes Increases Risk of Coronary Plaque Disruption and Thrombosis

Cause of Myocardial Infarction



Aspirin and diabetes in secondary prevention

Other high risk conditions:						
Haemodialysis	14	39/1333 (2.9)	67/1371 (4.9)	-12.2	23.4	41 (16)
Diabetes	9	403/2568 (15.7)	426/2558 (16.7)	-12.7	164.4	7 (8)
Carotid disease	6	36/339 (10.6)	43/337 (12.8)	-3.6	17.1	19 (22)
Subtotal	29	477/4240 (11.3)	536/4266 (12.6)	-28.5	204.9	13 (7)



Antiplatelet Trialists' Collaboration BMJ 2002;324:71-86

Proportional effects of aspirin on vascular events in high-risk patients

Aspirin dose

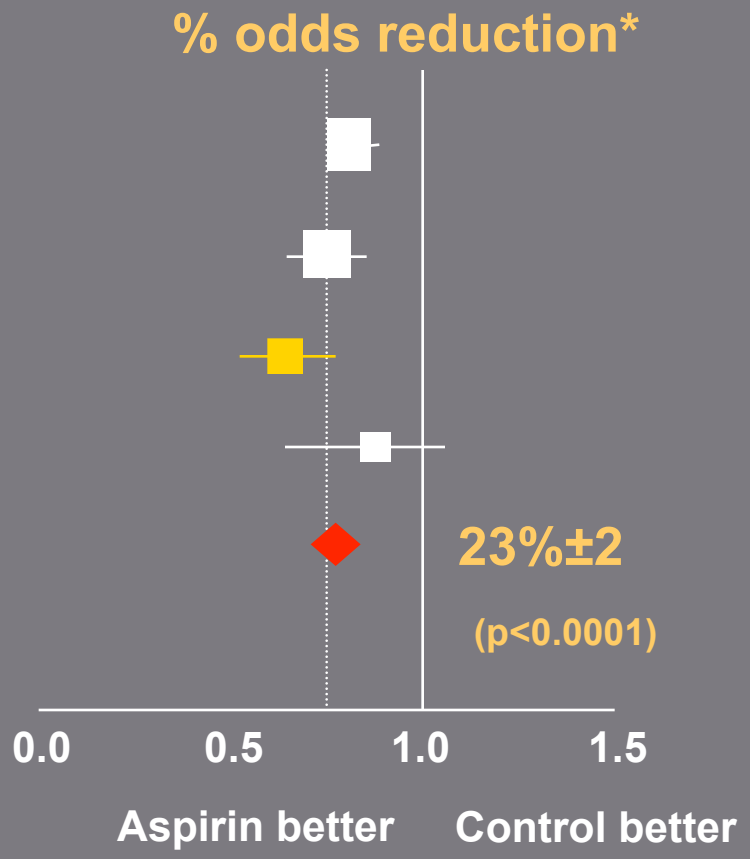
500–1500 mg daily

160–325 mg daily

75–150 mg daily

<75 mg daily

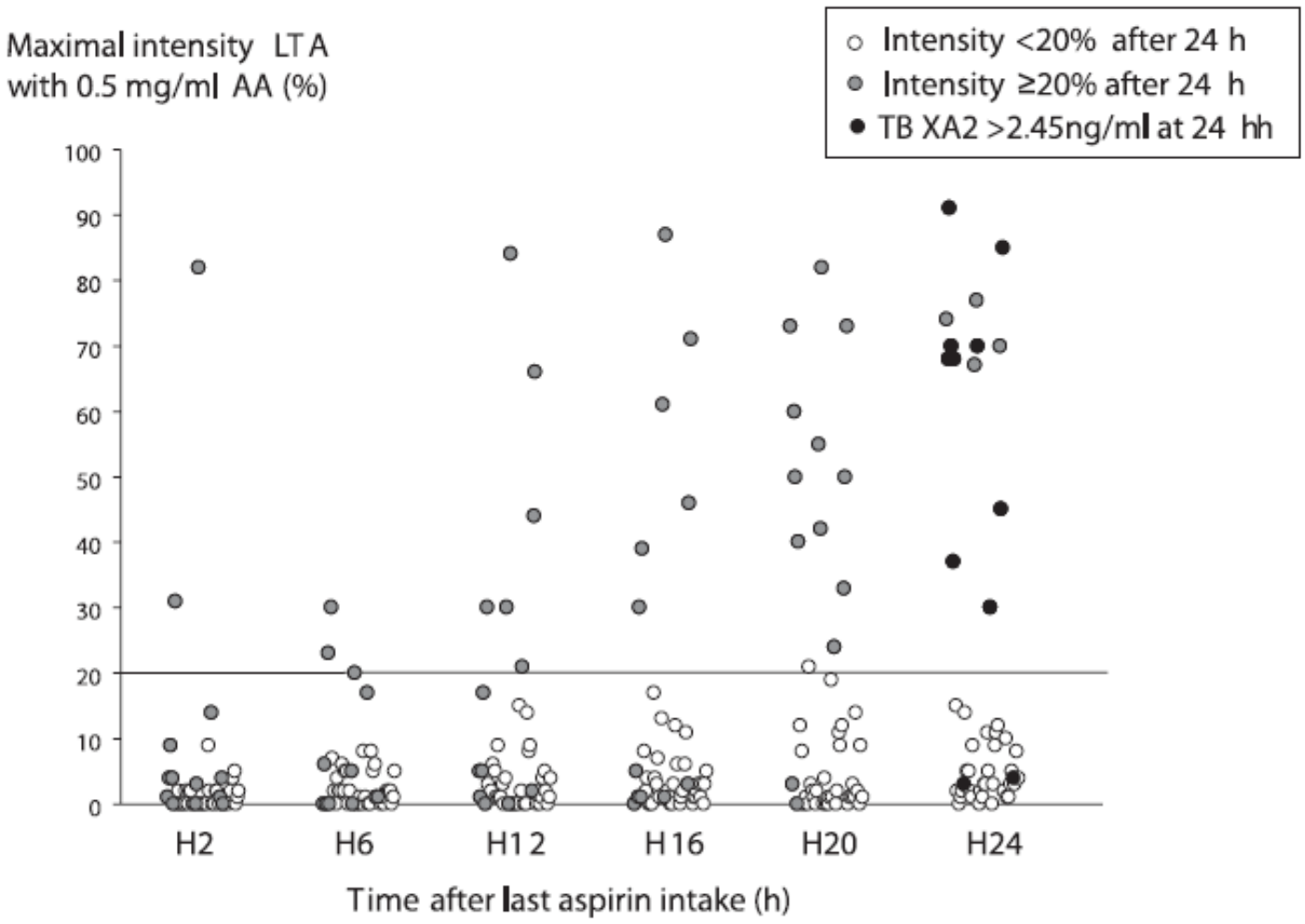
Any aspirin dose



***Vascular events: MI, stroke or vascular death**

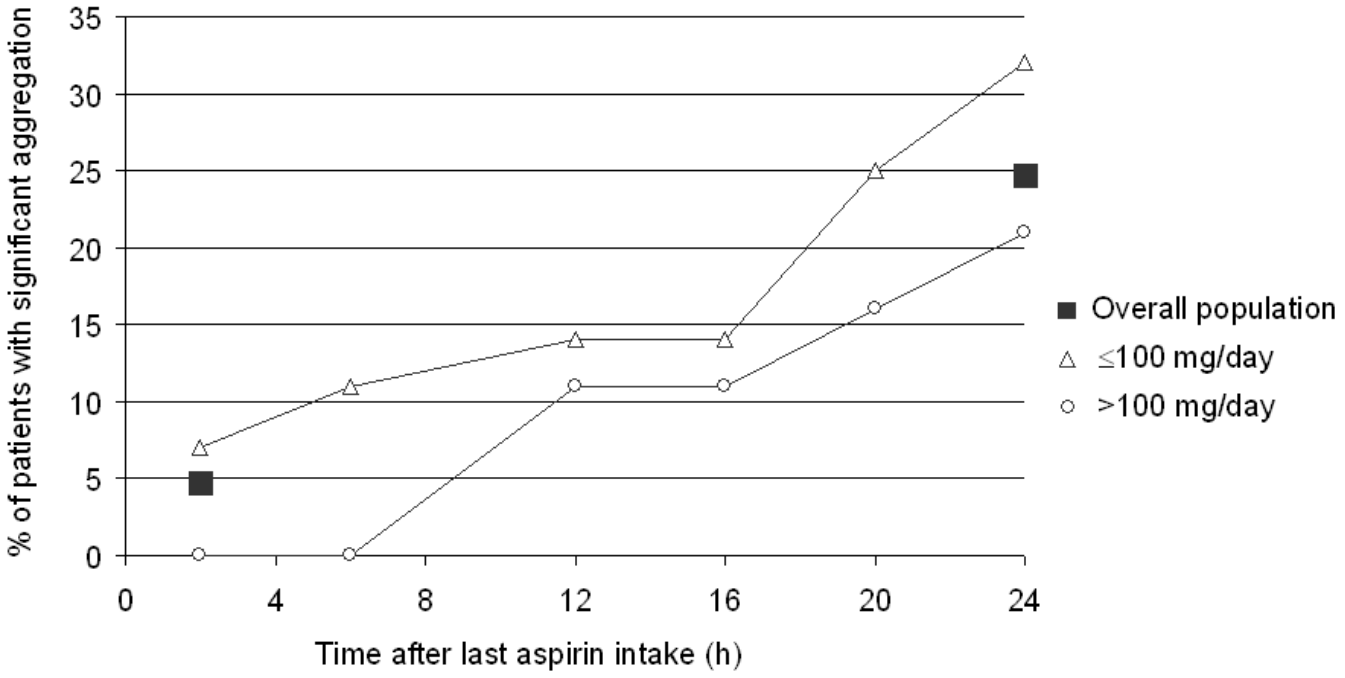
Antithrombotic Trialists' Collaboration. BMJ 2002;324:71

Accelerated turn-over



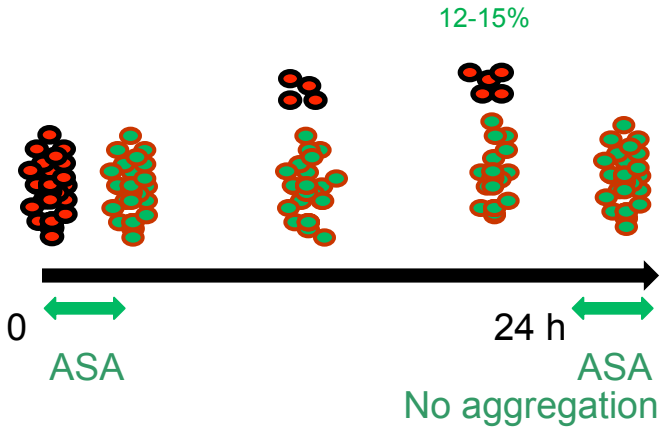
Henry et al. Thromb Haemost 2011;105: 336–44

Time dependance of aspirin

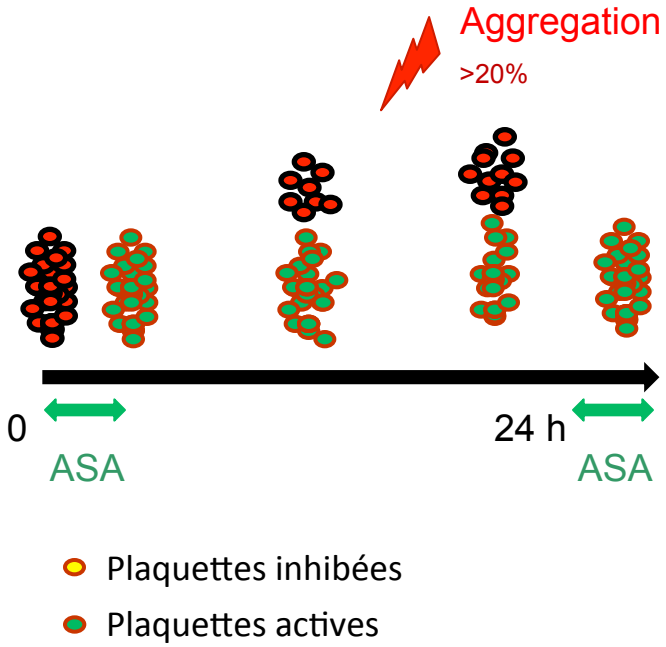


Henry et al, Thrombosis hemostasis, 2011

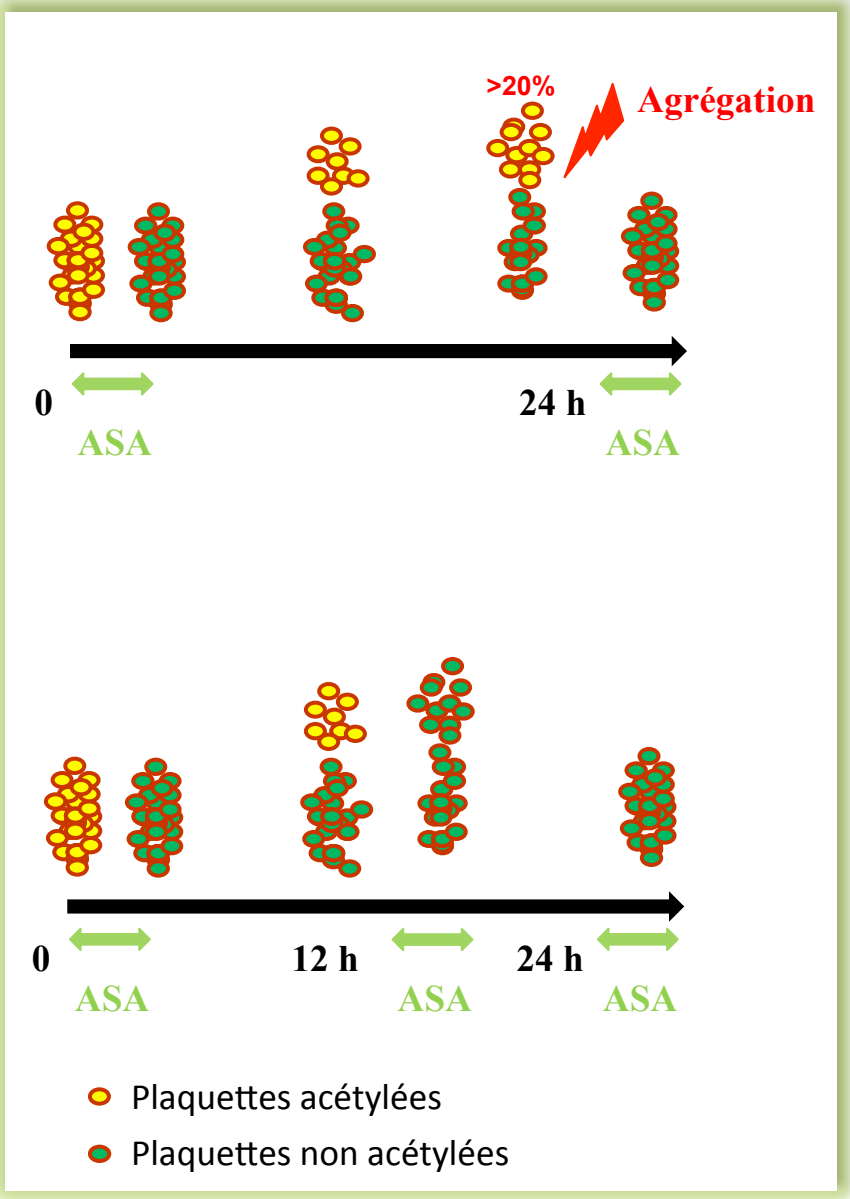
Normal turn over



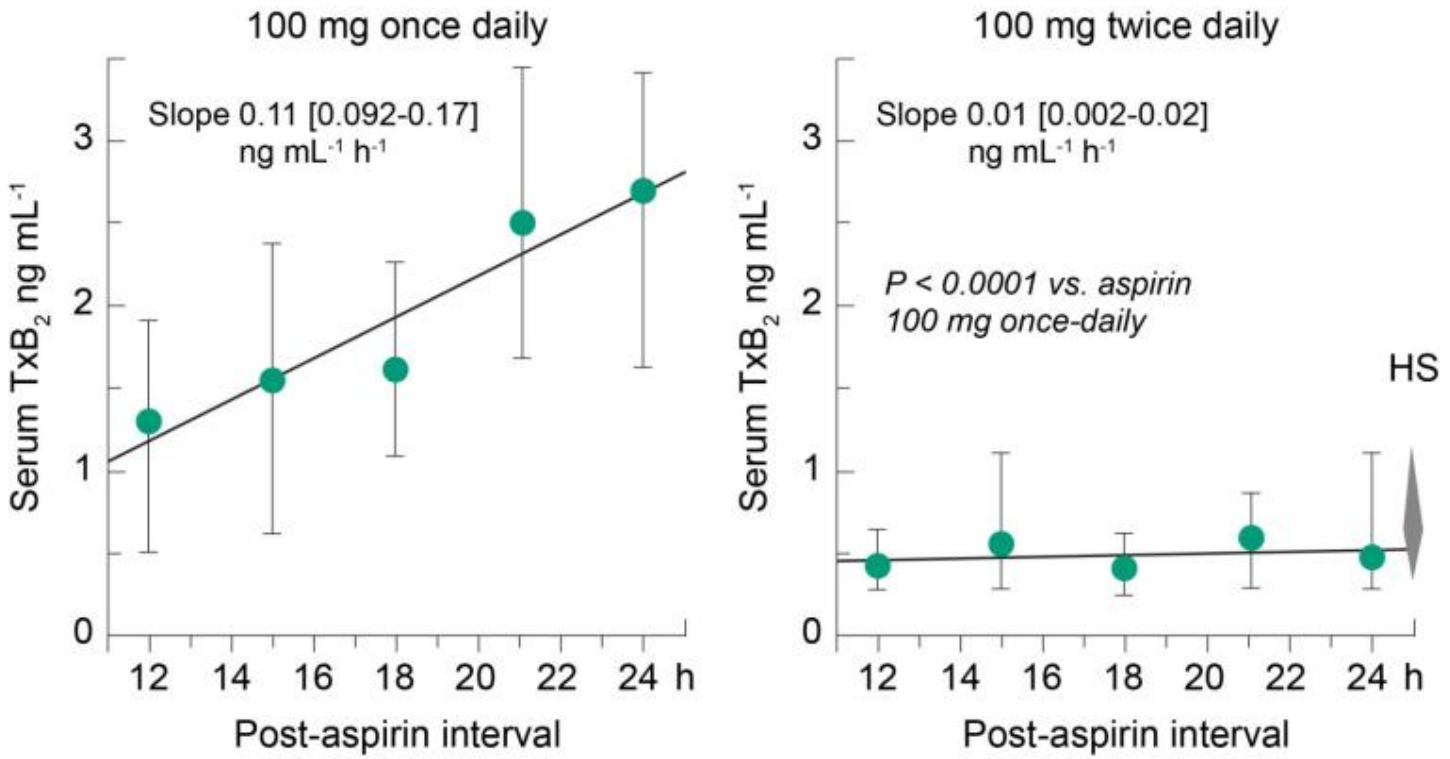
Accelerated turn over



Increasing aspirin intake

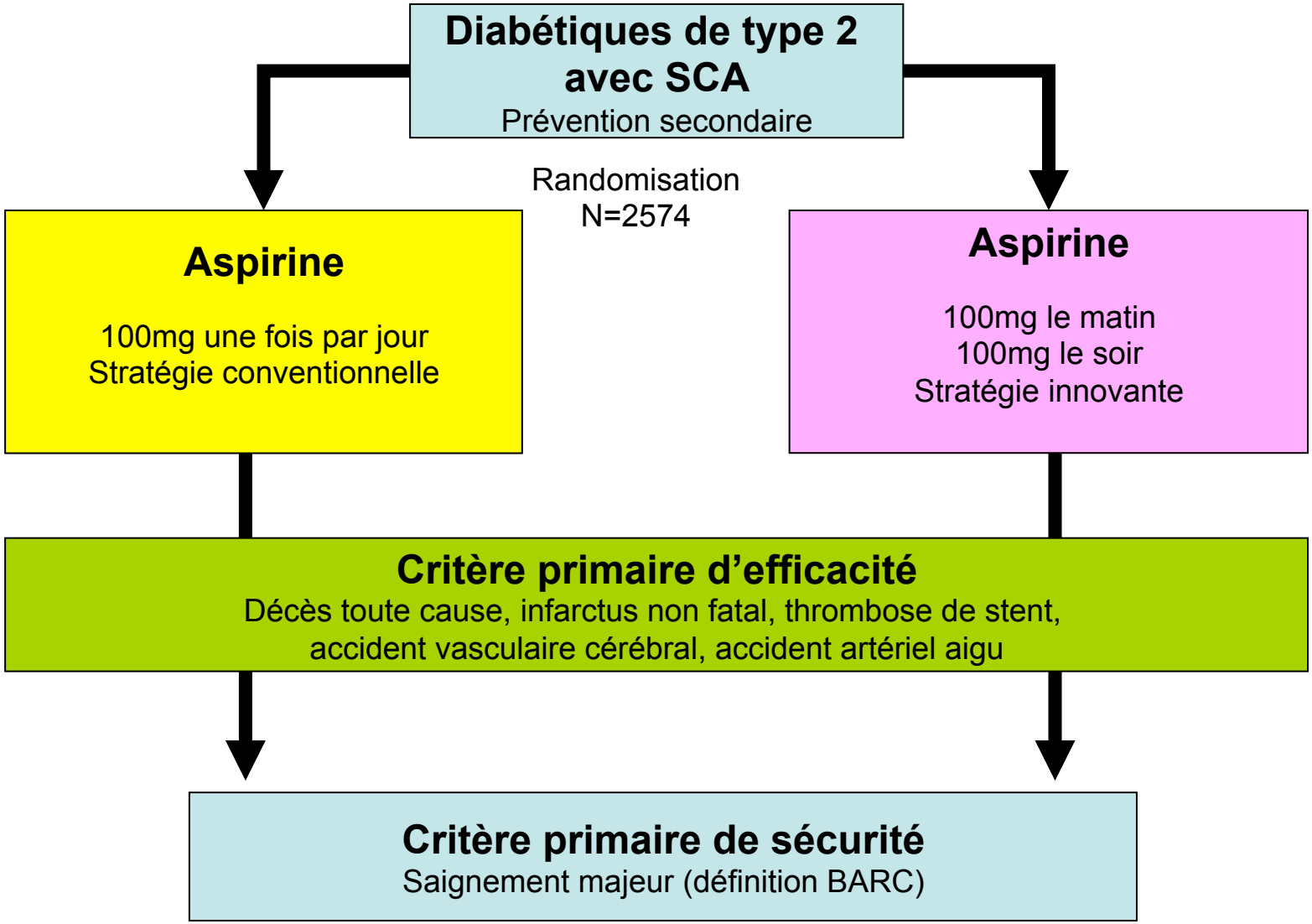


Could increased dosing frequency in diabetes overcome these issues?



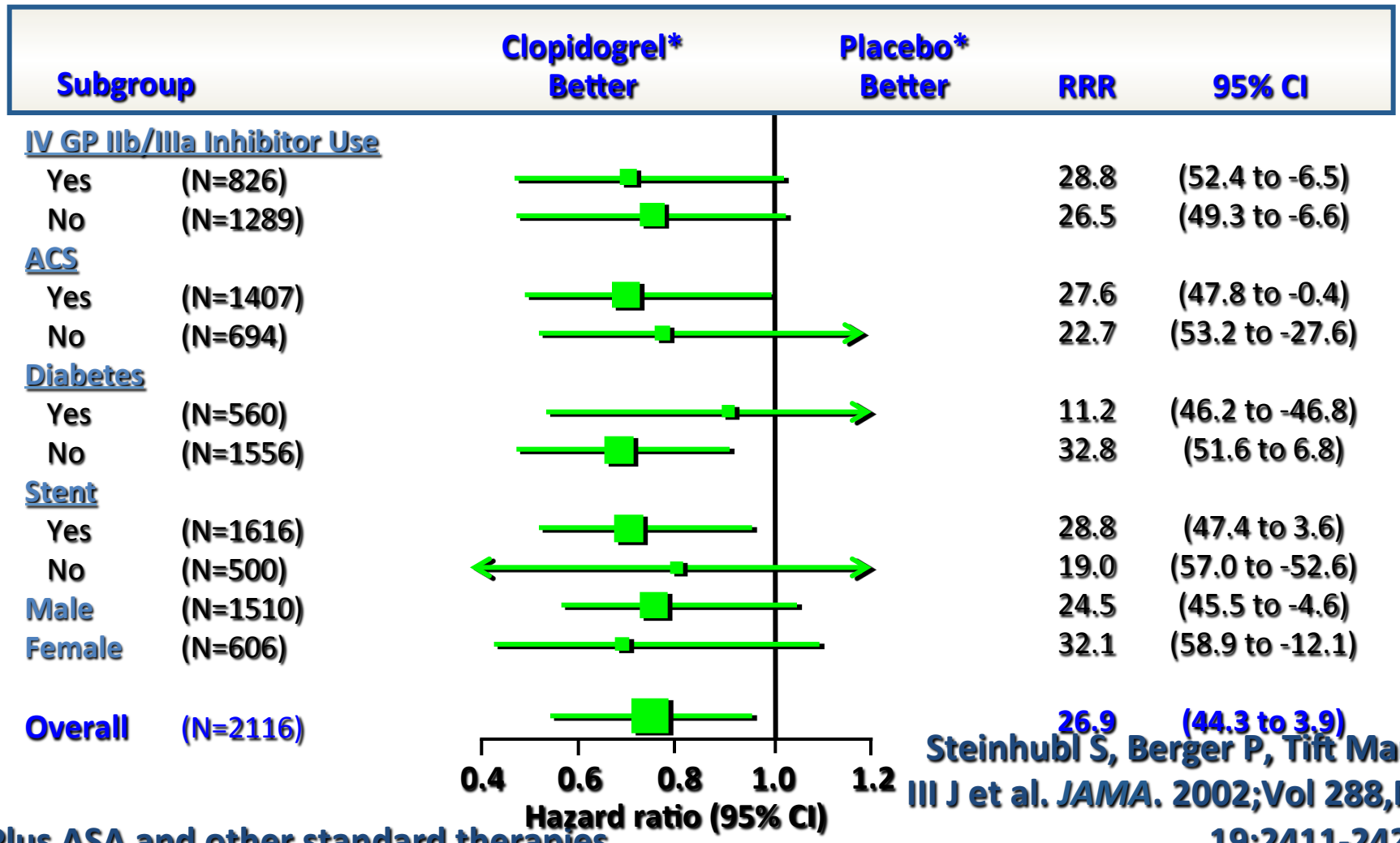
HS, healthy subjects.
Rocca B et al. J Thromb Haem 2012;10:1220-30.

Andaman Study



Suivi minimum 18 mois

CREDO : Long-Term Benefit of Clopidogrel: MI, Stroke, or Death at 1 Year



Steinhubl S, Berger P, Tift Mann III J et al. *JAMA*. 2002;Vol 288,No 19:2411-2420.

* Plus ASA and other standard therapies

TRITON: Diabetes Subgroup - Prasugrel

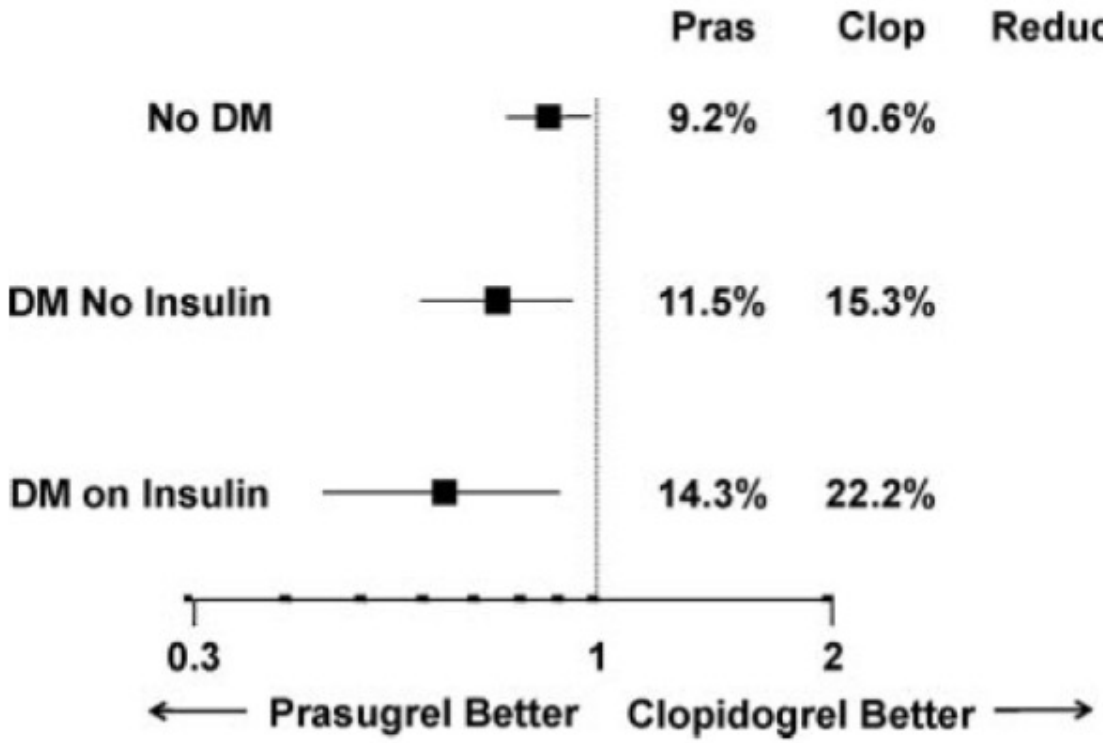
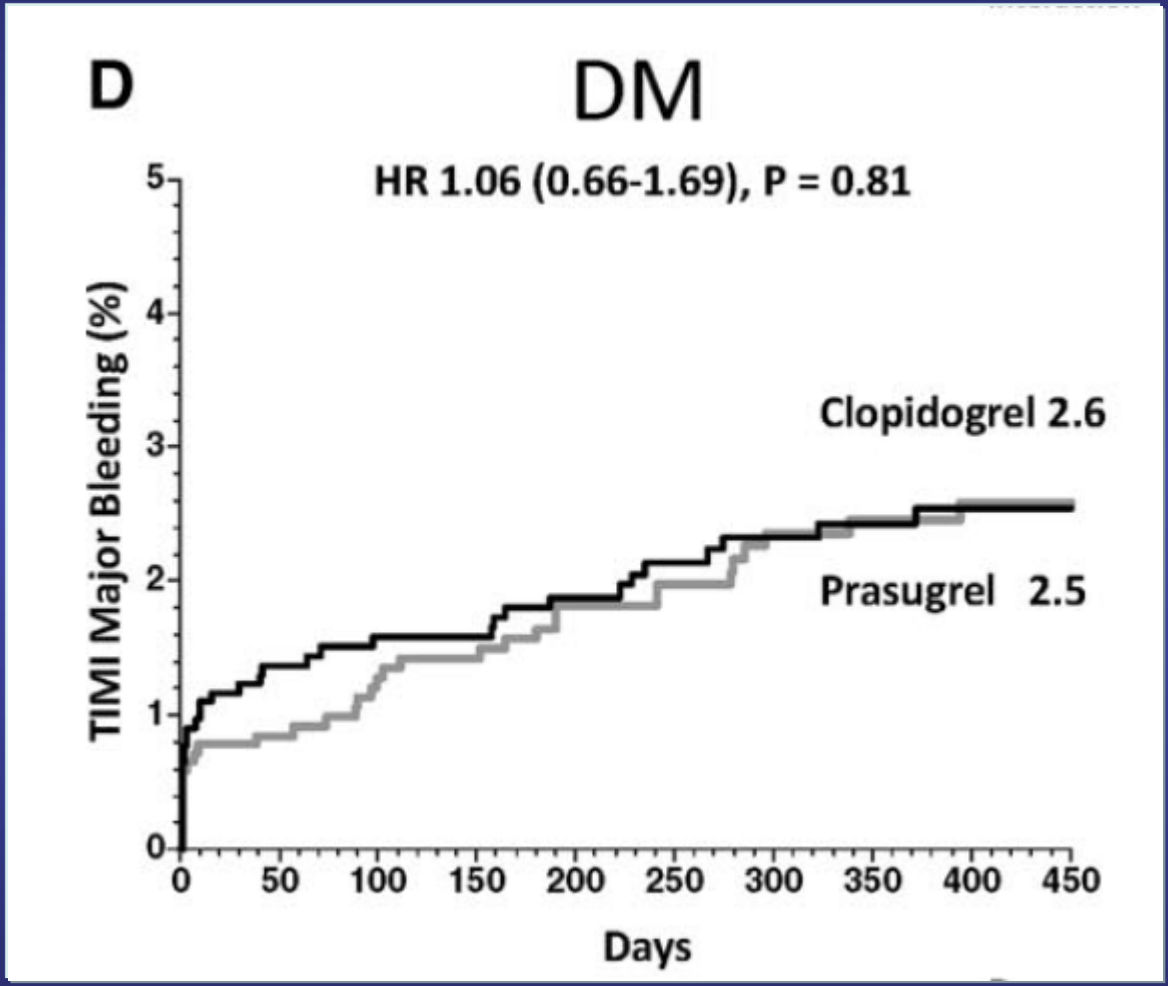


Figure 3. Reduction in the primary end point (cardiovascular death/nonfatal MI, nonfatal stroke) by diabetes status and treatment group. Pras indicates prasugrel; clop, clopidogrel.

TRITON Diabetes – Circulation 2010

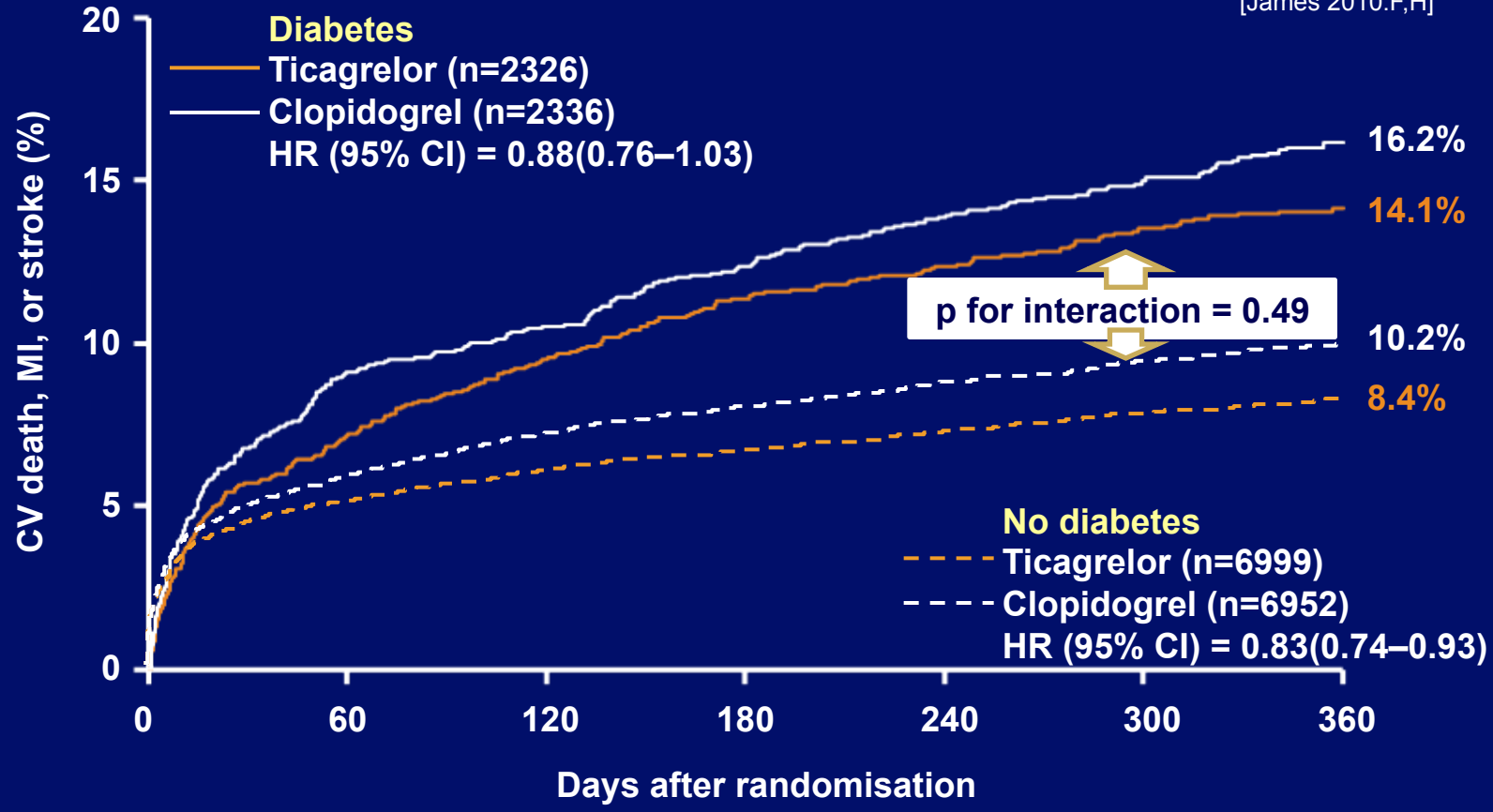
TRITON: Diabetes Subgroup - Prasugrel



TRITON Diabetes – Circulation 2010

PLATO diabetes: Primary composite endpoint

[James 2010:F,H]

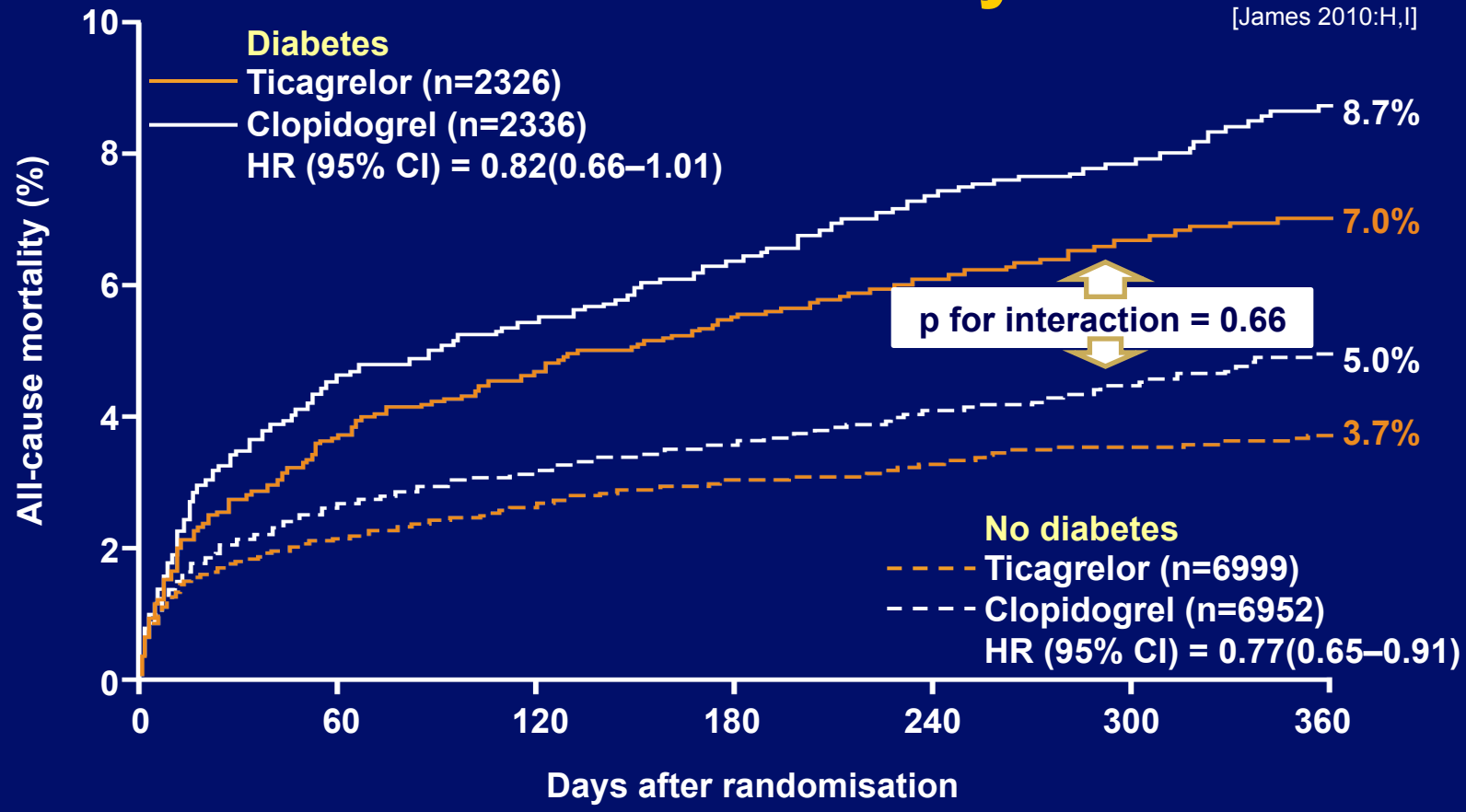


Primary endpoint benefit with ticagrelor was consistent with the overall PLATO trial results[Wallentin 2009:J]

No interaction between diabetes status and treatment was observed (p=0.49)[James 2010:G,H]

CI, confidence interval; CV, cardiovascular; HR, hazard ratio; MI, myocardial infarction.
James S, et al. *Eur Heart J* 2010;31:3006–3016.

PLATO diabetes: All-cause mortality



All-cause mortality benefit with ticagrelor was consistent with the overall PLATO trial results[Wallentin 2009:J]

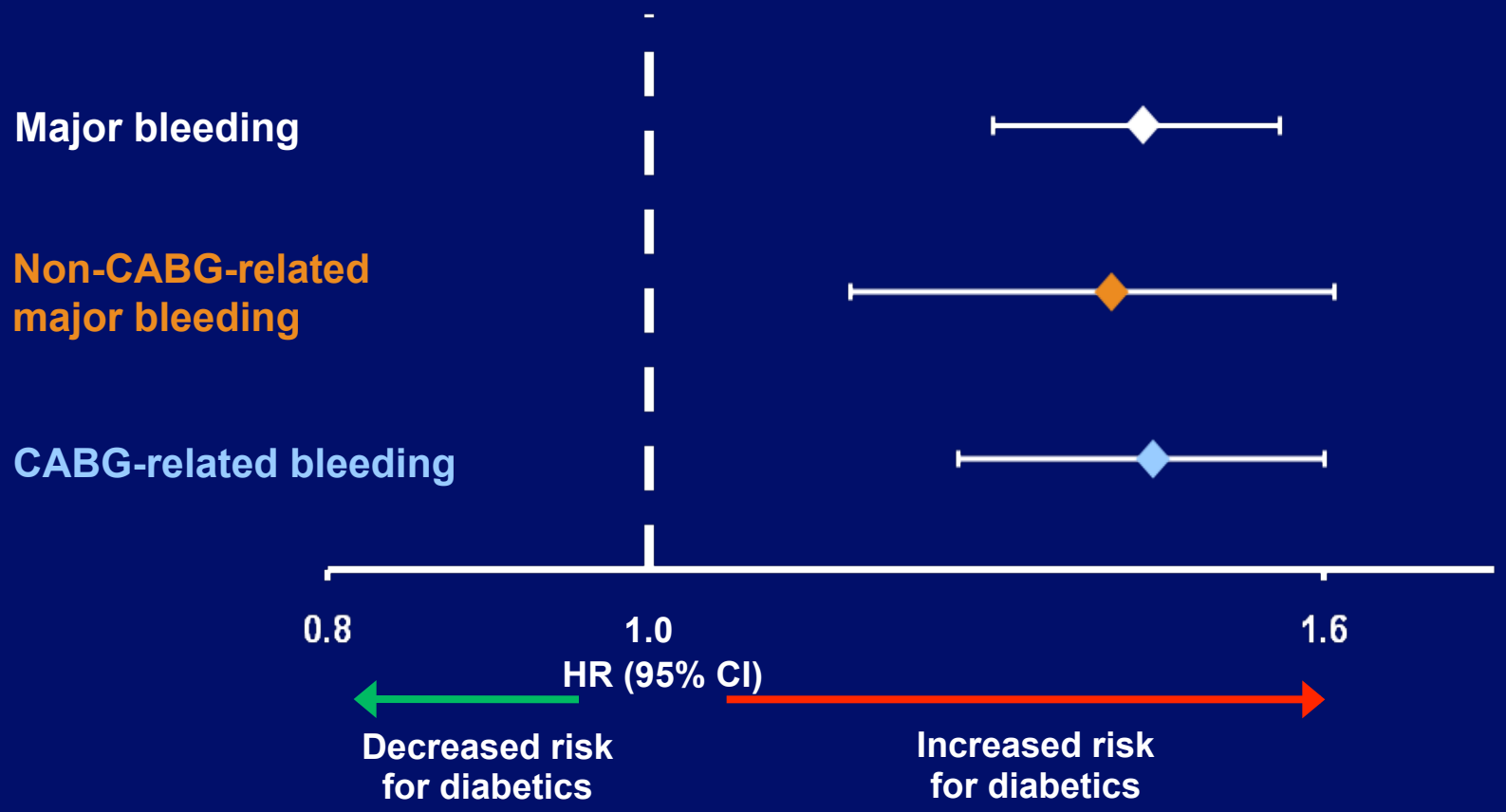
No interaction between diabetes status and treatment was observed (p=0.66)[James 2010:G,H]

CI, confidence interval; HR, hazard ratio.

James S, et al. *Eur Heart J* 2010;31:3006–3016.

Increased risk of bleeding events in diabetic patients

[James 2010:J]



CABG, coronary artery bypass graft.; CI, confidence interval; HR, hazard ratio.
James S, et al. *Eur Heart J* 2010;31:3006–3016.

Reduction in Ischemic Events With Ticagrelor in Diabetic Patients With Prior Myocardial Infarction in PEGASUS–TIMI 54

Deepak L. Bhatt, MD, MPH,[a] Marc P. Bonaca, MD, MPH,[a] Sameer Bansilal, MD, MS,[b] Dominick J. Angiolillo, MD, PhD,[c] Marc Cohen, MD,[d] Robert F. Storey, MD,[e] Kyungah Im, PhD,[a] Sabina A. Murphy, MPH,[a] Peter Held, MD, PhD,[f] Eugene Braunwald, MD,[a] Marc S. Sabatine, MD, MPH,[a] Ph. Gabriel Steg, MD[g]

ABSTRACT

BACKGROUND Patients with diabetes appear to be at elevated risk of atherothrombotic events.

OBJECTIVES The purpose of this study was to determine the effect of antiplatelet therapy with ticagrelor on recurrent ischemic events in patients with diabetes and prior myocardial infarction (MI).

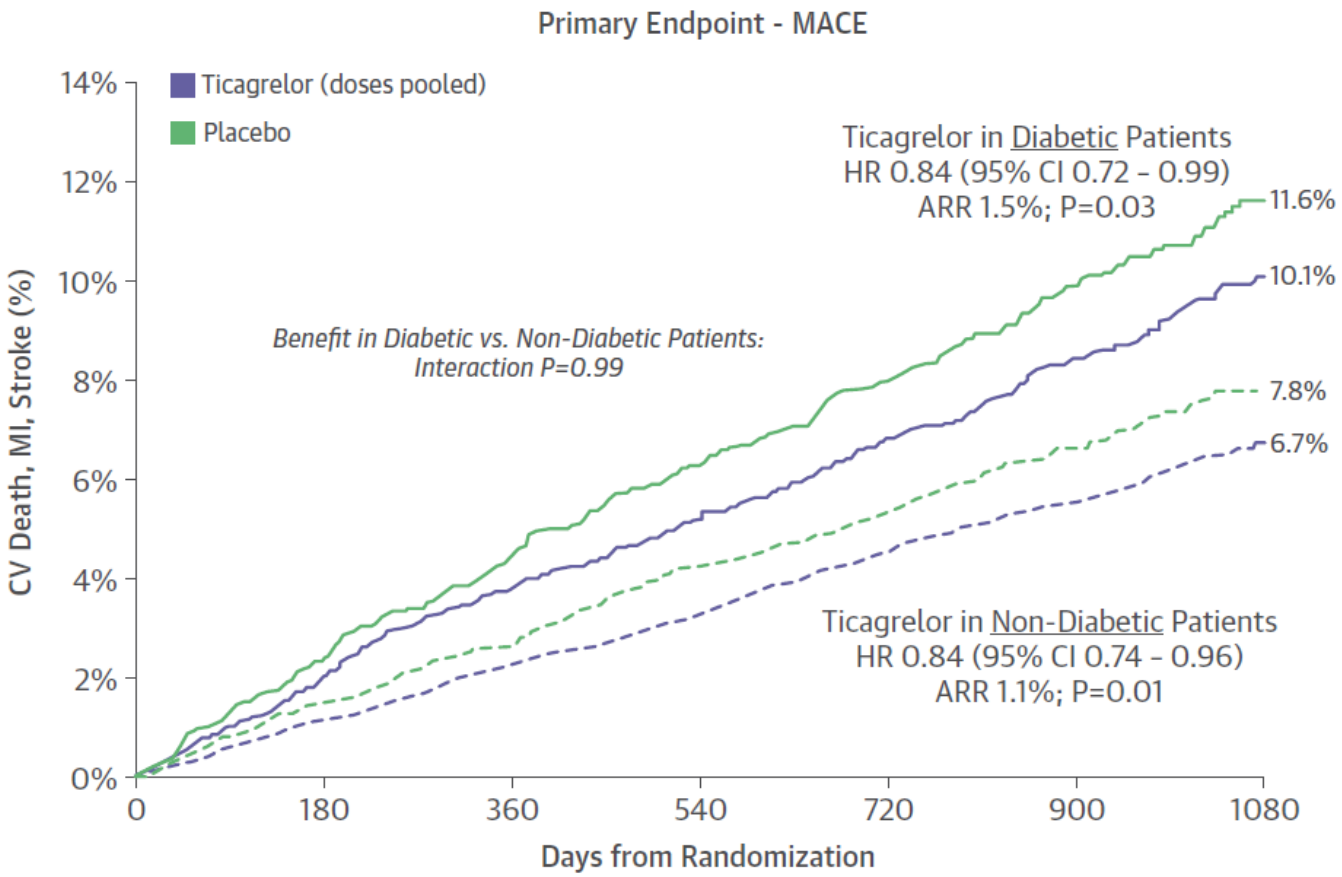
METHODS We examined the subgroups of patients with diabetes (n = 6,806) and without diabetes (n = 14,355) from PEGASUS-TIMI 54 (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin-Thrombolysis In Myocardial Infarction 54), in which 21,162 patients with a history of MI 1 to 3 years prior and with additional risk factors were randomized to ticagrelor (90 or 60 mg twice daily) or placebo. Patients were followed for a median of 33 months. The primary efficacy endpoint was major adverse cardiovascular events (MACE) (cardiovascular death, MI, stroke) and the primary safety endpoint was TIMI (Thrombolysis In Myocardial Infarction) major bleeding.

RESULTS The relative risk reduction in MACE with ticagrelor was consistent for the pooled doses versus placebo in patients with diabetes (hazard ratio [HR]: 0.84; 95% confidence interval [CI]: 0.72 to 0.99; p = 0.035) and without diabetes (HR: 0.84; 95% CI: 0.74 to 0.96; p = 0.013; p interaction = 0.99). As patients with diabetes were at higher risk of MACE, the absolute risk reduction tended to be greater in patients with versus without diabetes (1.5% vs. 1.1%, with corresponding 3-year number needed to treat of 67 vs. 91). In patients with diabetes requiring pharmacological therapy (n = 5,960), the absolute risk reduction was 1.9% with a 3-year number needed to treat of 53. Additionally, in patients with diabetes, ticagrelor reduced cardiovascular death by 22% and coronary heart disease death by 34%. Similar to patients without diabetes, there was increased TIMI major bleeding in patients with diabetes (HR: 2.56; 95% CI: 1.52 to 4.33; p = 0.0004).

CONCLUSIONS In patients with diabetes with prior MI, adding ticagrelor to aspirin significantly reduces the risk of recurrent ischemic events, including cardiovascular and coronary heart disease death. (Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin [PEGASUS]; NCT01225562) (J Am Coll Cardiol 2016;67:2732-40) © 2016 by the American College of Cardiology Foundation.

Bhatt et al, JACC 2016;67:2732-40

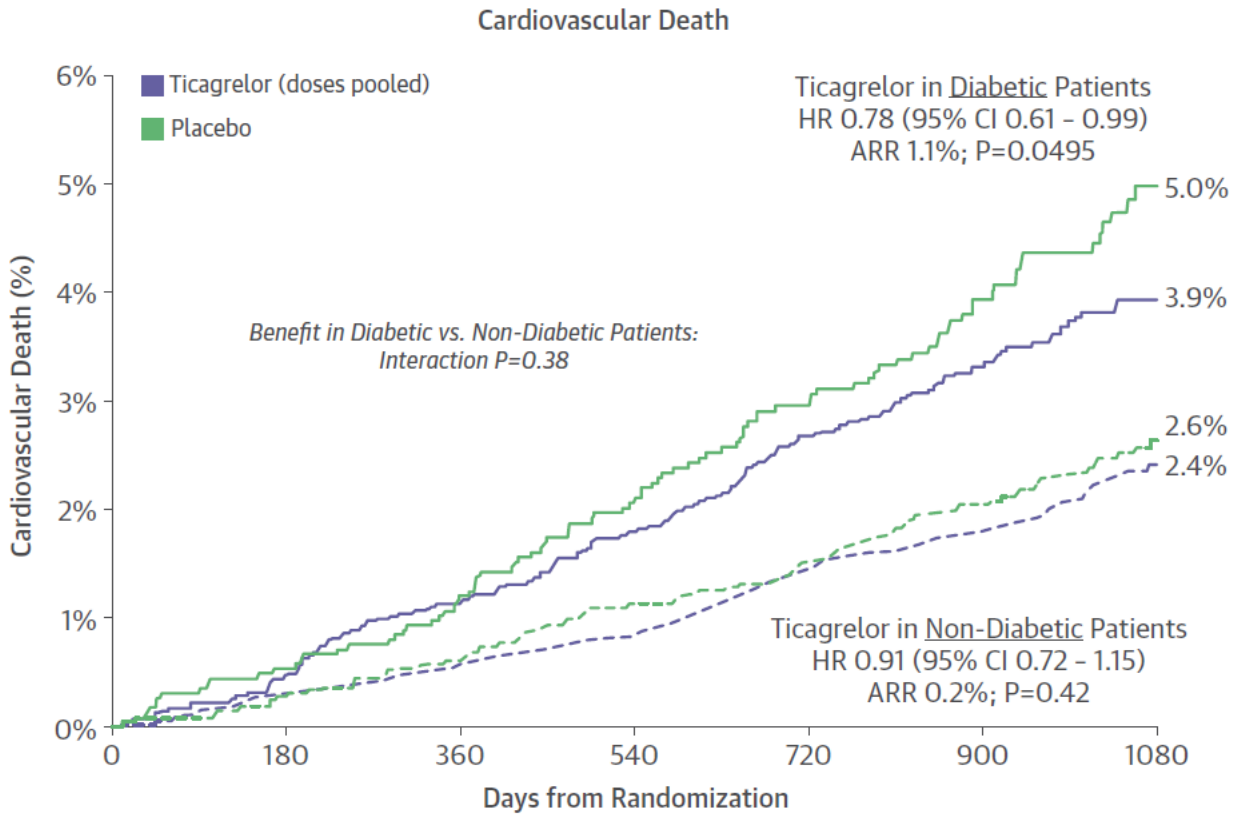
FIGURE 1 Rates of MACE in the Pooled Ticagrelor Versus Placebo Arms For Patients With and Without Diabetes



ARR = absolute risk reduction; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; ITT = intention to treat; MACE = major adverse cardiovascular events; MI = myocardial infarction.

Bhatt et al, JACC 2016;67:2732-40

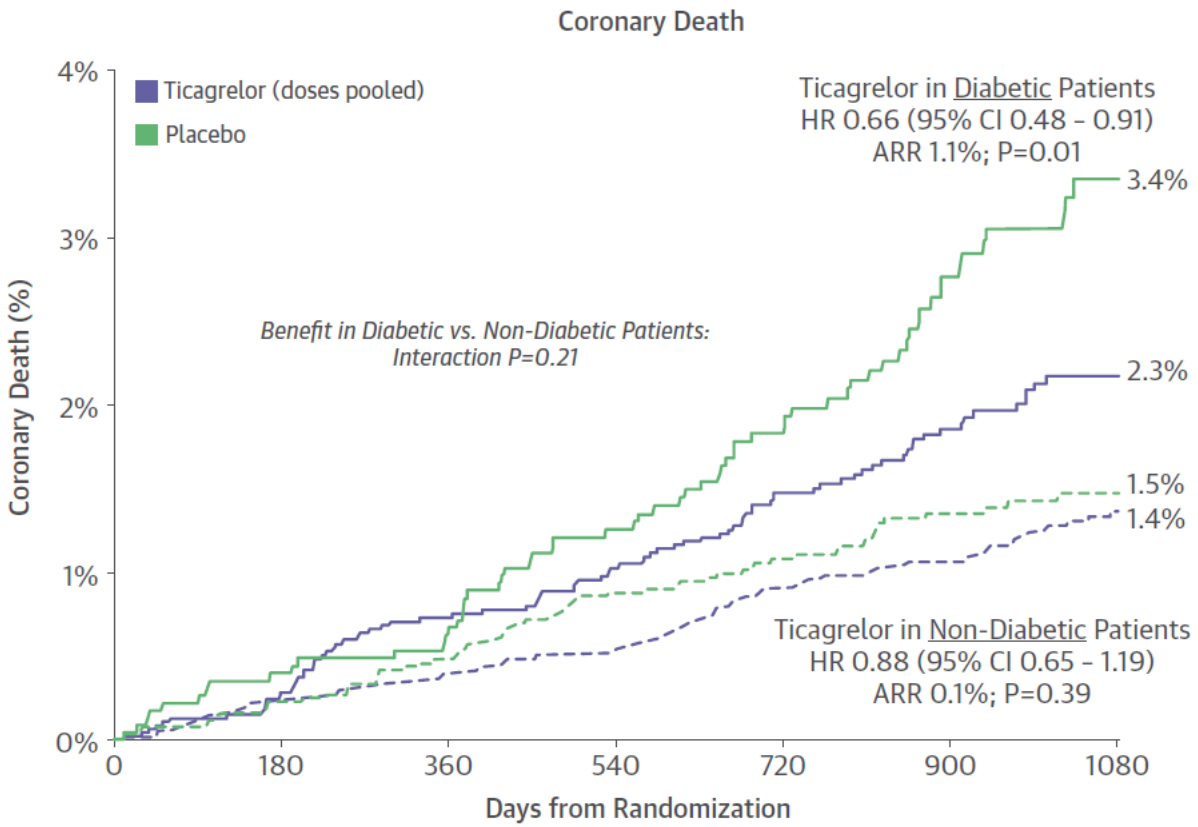
FIGURE 2 Rates of CV Deaths in the Pooled Ticagrelor Versus Placebo Arms for Patients With and Without Diabetes



Abbreviations as in Figure 1.

Bhatt et al, JACC 2016;67:2732-40

FIGURE 3 Rates of Coronary Deaths in the Pooled Ticagrelor Versus Placebo Arms for Patients With and Without Diabetes



Abbreviations as in Figure 1.

Bhatt et al, JACC 2016;67:2732-40

TABLE 3 Individual Efficacy and Safety Endpoints Versus Placebo for the Pooled Ticagrelor Doses, 90-mg Dose, and 60-mg Dose in Patients With Diabetes

	Ticagrelor Dose	Placebo	Hazard Ratio (95% CI)	p Value
Pooled Ticagrelor Doses				
Efficacy	(n = 4,549)	(n = 2,257)		
MACE	10.08	11.60	0.84 (0.72-0.99)	0.0348
CV death	3.92	4.97	0.78 (0.61-0.99)	0.0495
MI	5.88	6.51	0.89 (0.72-1.10)	0.28
Stroke	1.79	2.46	0.69 (0.49-0.99)	0.0447
All-cause death	6.23	7.11	0.86 (0.70-1.05)	0.15
CHD death	2.18	3.35	0.66 (0.48-0.91)	0.011
Safety	(n = 4,497)	(n = 2,238)		
TIMI major bleeding	2.56	0.98	2.56 (1.52-4.33)	0.0004
TIMI major or minor bleeding	3.76	1.32	2.91 (1.84-4.59)	<0.0001
Ticagrelor 90-mg Dose				
Efficacy	(n = 2,241)	(n = 2,257)		
MACE	10.14	11.60	0.85 (0.71-1.03)	0.0934
CV death	4.07	4.97	0.82 (0.62-1.10)	0.19
MI	5.79	6.51	0.88 (0.68-1.13)	0.31
Stroke	1.82	2.46	0.69 (0.45-1.06)	0.0914
All-cause death	6.28	7.11	0.88 (0.70-1.12)	0.30
CHD death	2.22	3.35	0.68 (0.47-0.99)	0.0491
Safety	(n = 2,216)	(n = 2,238)		
TIMI major bleeding	2.62	0.98	2.67 (1.52-4.71)	0.0007
TIMI major or minor bleeding	4.34	1.32	3.48 (2.15-5.63)	<0.0001
Ticagrelor 60-mg Dose				
Efficacy	(n = 2,308)	(n = 2,257)		
MACE	10.00	11.60	0.83 (0.69-1.004)	0.0547
CV death	3.79	4.97	0.74 (0.55-0.99)	0.0428
MI	5.97	6.51	0.90 (0.70-1.15)	0.39
Stroke	1.77	2.46	0.69 (0.46-1.06)	0.0906
All-cause death	6.18	7.11	0.84 (0.66-1.06)	0.15
CHD death	2.14	3.35	0.64 (0.43-0.94)	0.0214
Safety	(n = 2,281)	(n = 2,238)		
TIMI major bleeding	2.51	0.98	2.47 (1.40-4.35)	0.0018
TIMI major or minor bleeding	3.22	1.32	2.39 (1.45-3.94)	0.0007

Values are 3-year Kaplan-Meier event rates expressed as % unless otherwise indicated.

CHD = coronary heart disease; CI = confidence interval; CV = cardiovascular; MACE = major adverse cardiovascular events; MI = myocardial infarction; TIMI = Thrombolysis In Myocardial Infarction.

TIMI Major
Pegasus all

Tica 90 : 2,60

Placebo 1,06

Tica 60 : 2,30

Bhatt et al, JACC 2016;67:2732-40

- Mr Z, diabétique de type 2 a été hospitalisé pour **récidive** de syndrome coronaire aigu avec sus decalage du segment ST.

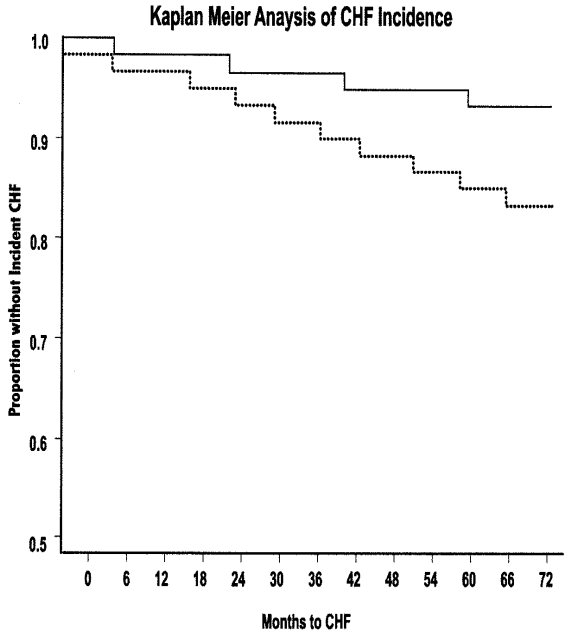
- Traitement à l'entrée : Kardegic 75 mg, atorvastatine 10 mg, metformine 3000 mg/j

- Excellent résultat de l'angioplastie marginale. Angioplastie de l'IVA proximale avec un stent. Lésions diffuses

- Traitement de sortie: Kardegic 75 mg, ticagrelor (1 an), atorvastatine 10 mg, metformine 3000 mg/j

Insuffisance cardiaque

Risque d'insuffisance cardiaque chez le diabétique



The Incidence of Congestive Heart Failure in Type 2 Diabetes

An update

Cohorte USA (Kaiser), matchée
- 8845 non diabétiques
- 8231 diabétiques type 2

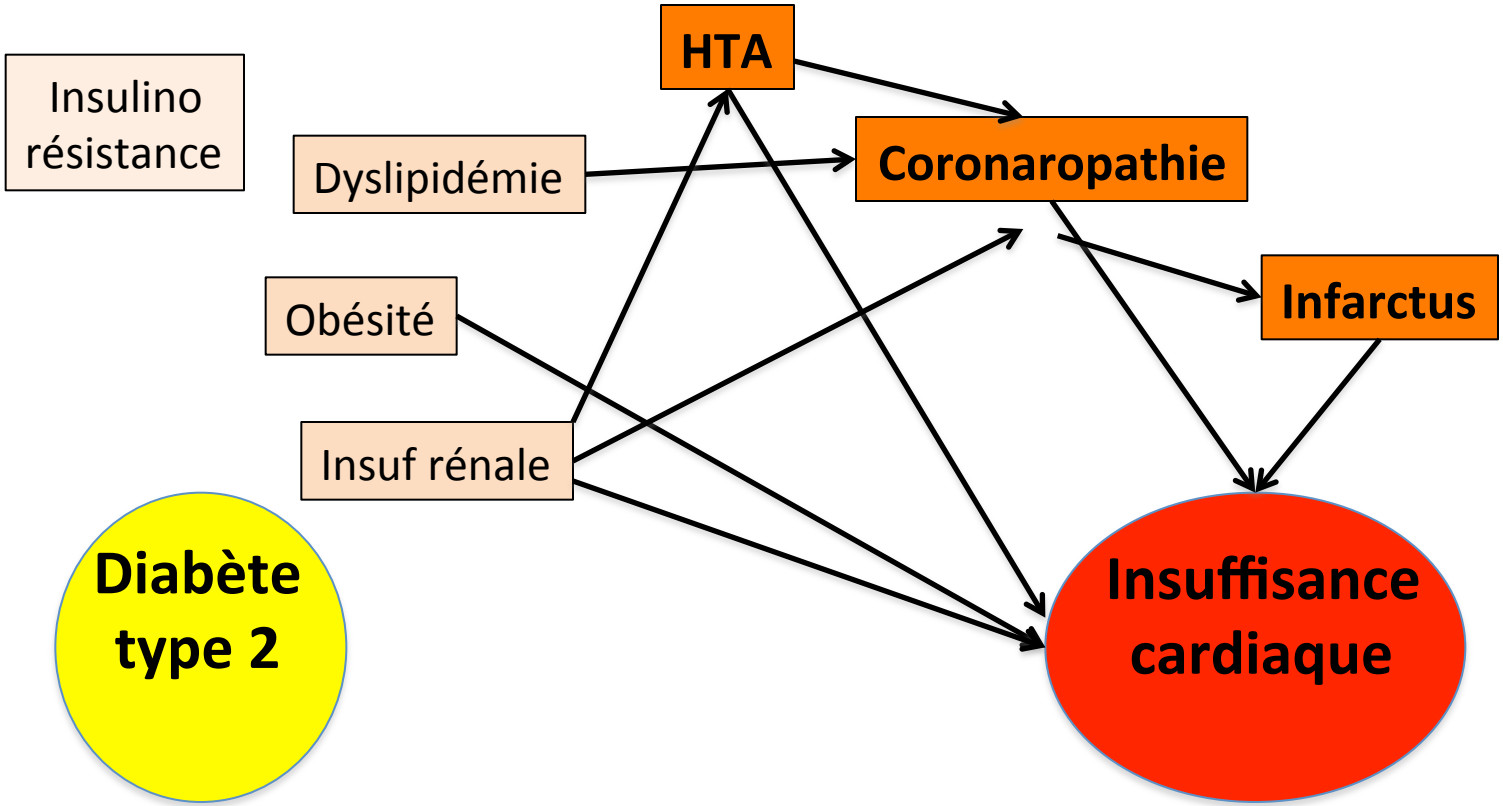
Chez diabétique
- 2,5 x plus fréquent
- 1% / an

Diabetes Care 2004

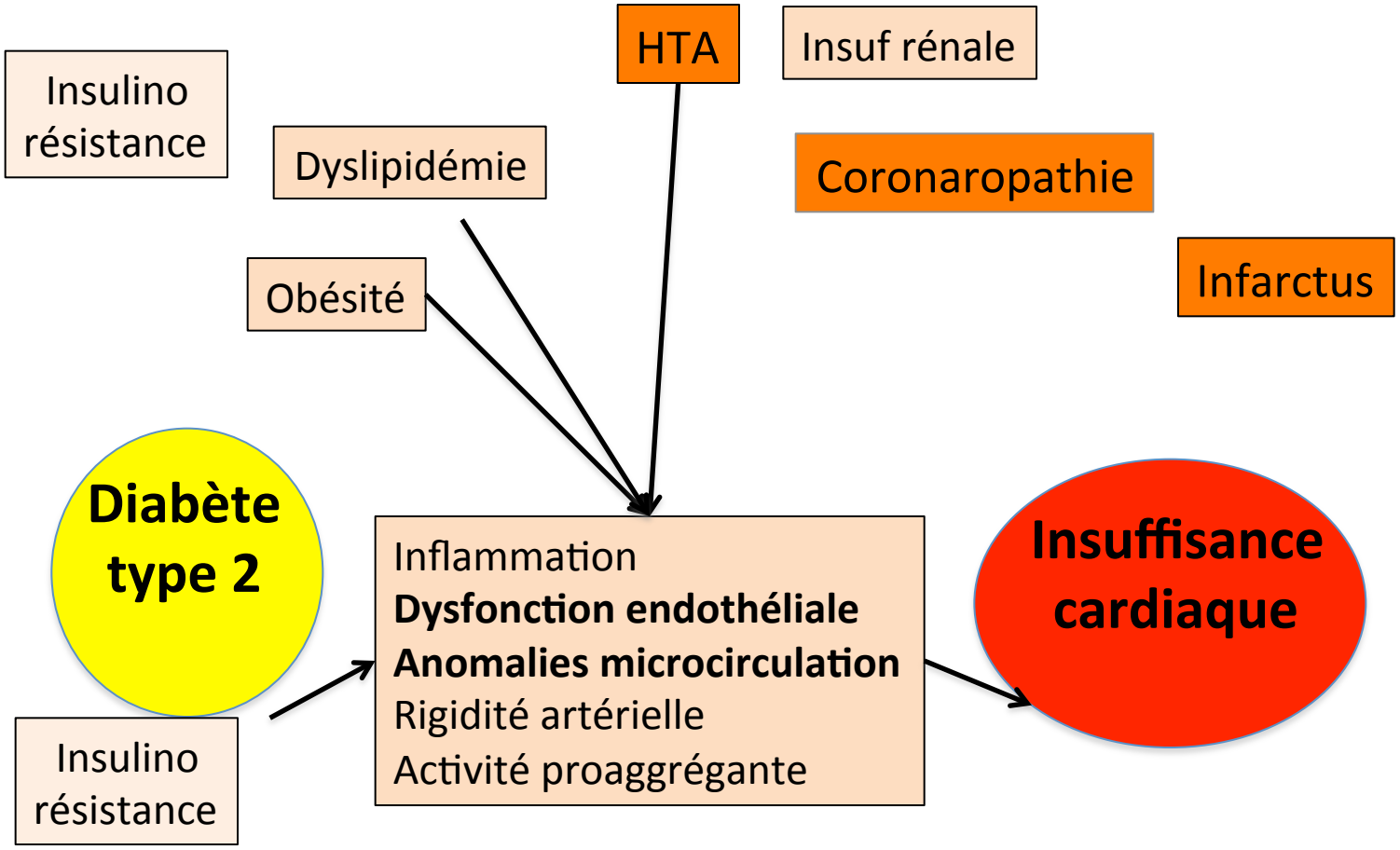
Table 2—*Six-year CHF incidence per 1,000 person-years by age-group*

Age	Diabetic patients	Nondiabetic patients	Rate ratio	95% CI
<45 years	4.5	0.4	11.0	5.6–21.8
45–54 years	11.9	1.4	8.6	6.4–11.4
55–64 years	23.6	5.0	4.7	3.9–5.8
65–74 years	38.7	13.7	2.8	2.4–3.3
75–84 years	63.9	34.7	1.8	1.6–2.2
85–94 years	97.8	78.8	1.2	0.8–1.8
95+ years	59.5	110.4	0.5	0.1–2.2
All	30.9	12.4	2.5	2.3–2.7

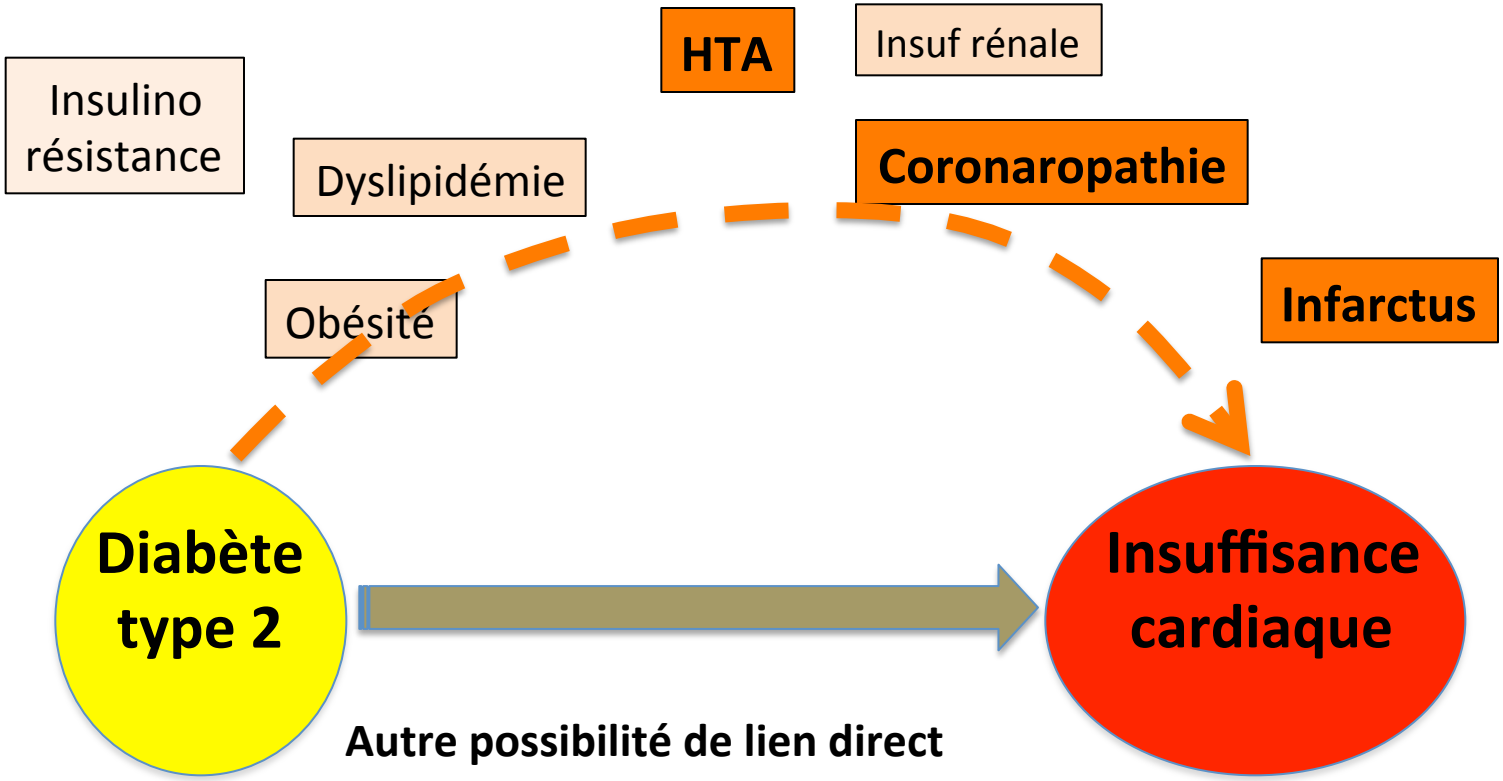
Du diabète à l'insuffisance cardiaque: quels mécanismes?



Du diabète à l'insuffisance cardiaque: quels mécanismes?



Du diabète à l'insuffisance cardiaque: quels mécanismes?



Autre possibilité de lien direct

➔ cardiomyopathie diabétique

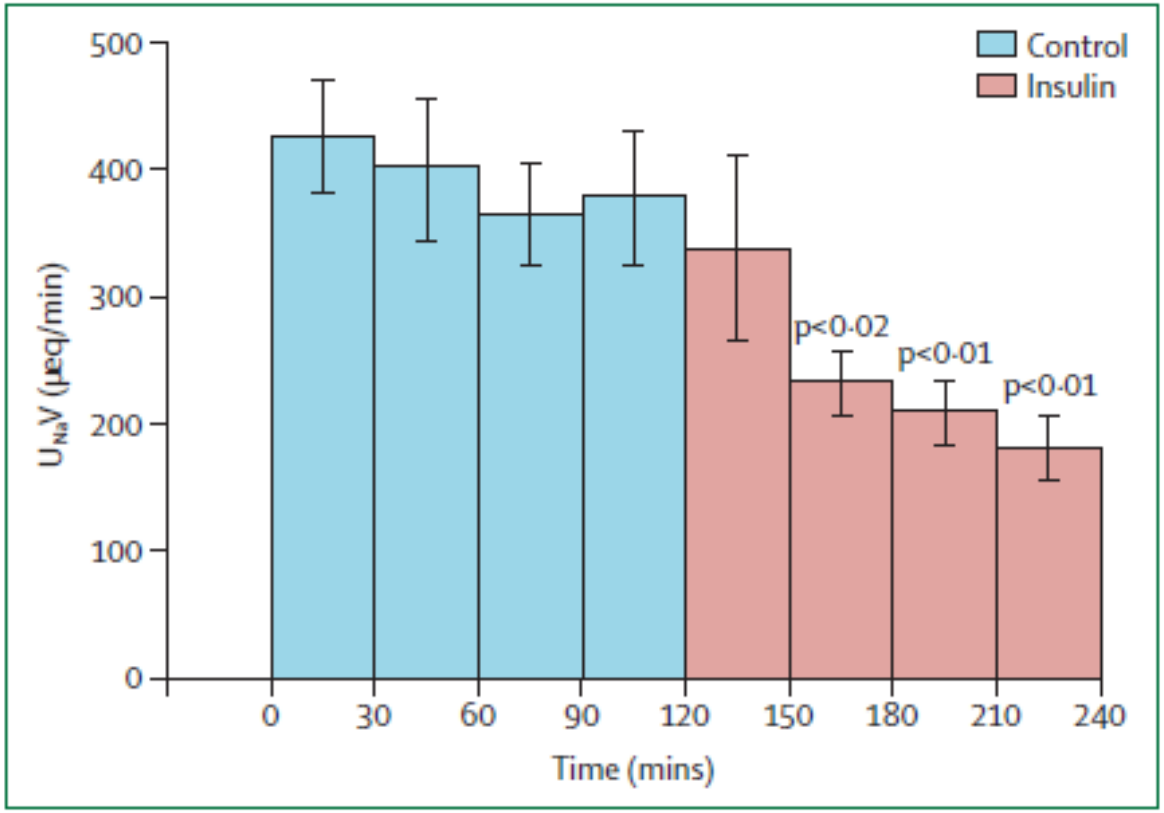
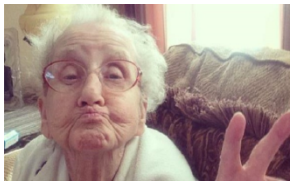


***Figure 5*: Time course of fall in urinary sodium excretion ($U_{Na}V$) during insulin administration**

Bars show mean values of six patients with standard error of the mean (SEM). Plasma insulin concentrations during insulin infusion were constant for each patient (range for the group was 98–193 μU/mL). Steady-state water diuresis was maintained throughout control and insulin administration periods. Reproduced with permission from De Fronzo and colleagues.[71]

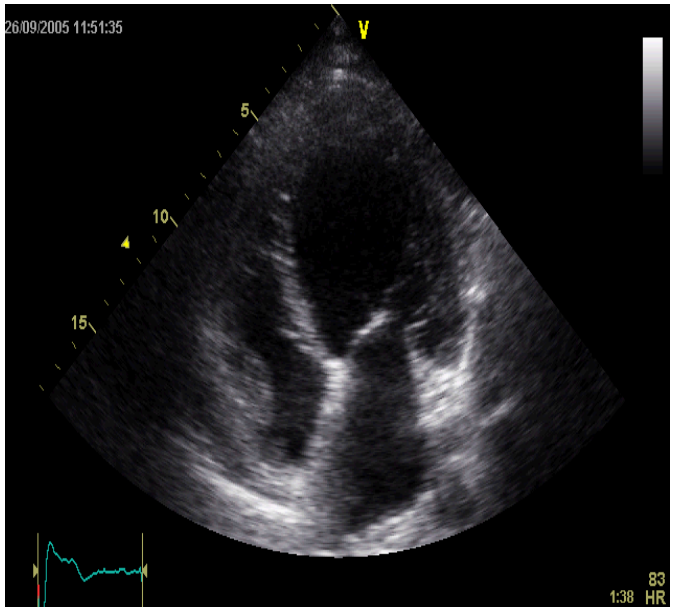
Insuffisance cardiaque et FEVG



50% des IC

40% des IC

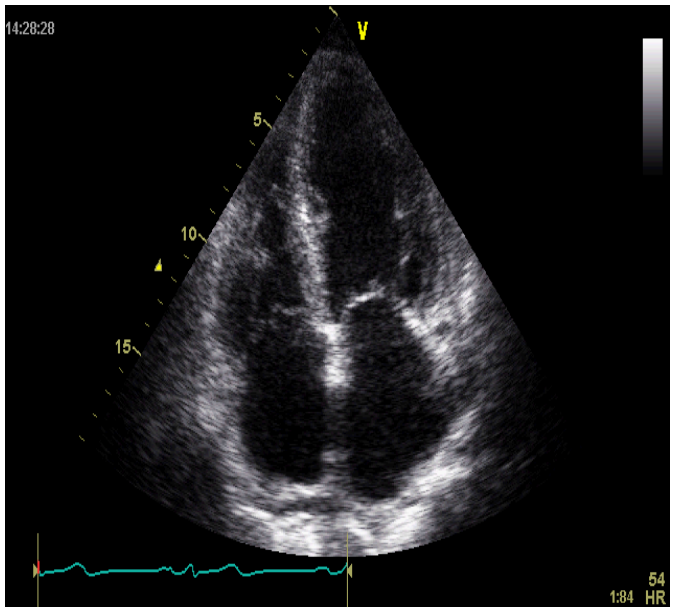
FEVG Réduite (<40%)



Post-infarctus, CMD …

- Dilatation VG +- HVG
- Activation hormonale +++

FEVG Préservée (≥ 50%)



HTA, RAo, diabète, obésité
Vieillissement++
- Pas de dilatation mais HVG
- Moindre activation hormonale

IC et diabète : efficacité des IEC ?

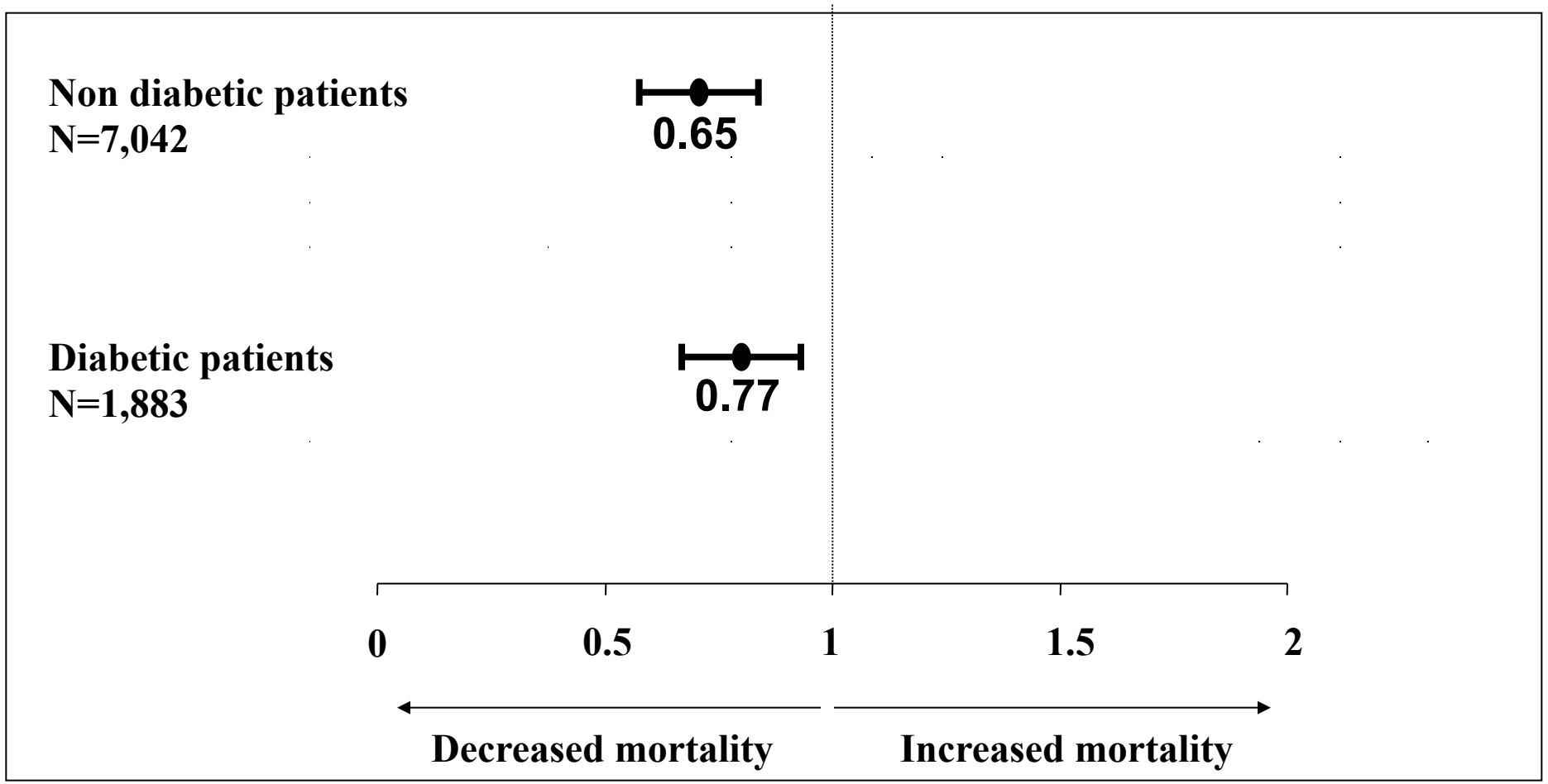
Shekelle (Metaanalysis). J Am Coll Cardiol 2003

ACE Inhibitors in Diabetic and Nondiabetic Patients with Heart Failure

Etude	Total N	Non-diabétiques	Diabetiques	Risque relatif, Non-diabétiques (95% IC)	Risque relatif Diabétiques (95% IC)	Rapport des Risques Relatifs (95% IC)
CONSENSUS	**253**	**197**	**56**	**0,64 (0,46, 0,88)**	**1,06 (0,65, 1,74)**	**1,67 (0,93, 3,01)**
SAVE	**2231**	**1739**	**492**	**0,82 (0,68, 0,99)**	**0,89 (0,68, 1,16)**	**1,09 (0,79, 1,50)**
SMILE	**1556**	**1253**	**303**	**0,79 (0,54, 1,15)**	**0,44 (0,22, 0,87)**	**0,56 (0,25, 1,22)**
SOLVD-prevention	**4228**	**3581**	**647**	**0,97 (0,83, 1,15)**	**0,75 (0,55, 1,02)**	**0,77 (0,54, 1,09)**
SOLVD-treatment	**2569**	**1906**	**663**	**0,84 (0,74, 0,95)**	**1,01 (0,85, 1,21)**	**1,21 (0,97, 1,50)**
TRACE	**1749**	**1512**	**237**	**0,85 (0,74, 0,97)**	**0,73 (0,57, 0,94)**	**0,87 (0,65, 1,15)**
Estimation globale		**10188**	**2398**	**0,85 (0,78, 0,92)**	**0,84 (0,70, 1,00)**	**1,00 (0,80, 1,25)**

Shekelle P et al. *J Am Coll Cardiol*. 2003;41:1529-1538.

IC et diabète : efficacité des bétabloqueurs?



Shekelle (Metaanalysis). J Am Coll Cardiol 2003

EMPHASIS-HF

NYHA Class II HF (N=2737)
LV EF < 30%
Eplerenone 25-50mg QD vs. Placebo

EMPHASIS-HF: Major results

Outcome	Eplerenone (%)	Placebo (%)	Adjusted hazard ratio (95% CI)	p
Cardiovascular death/heart-failure hospitalization	18.3	25.9	0.63 (0.54–0.74)	<0.001
Cardiovascular death	10.8	13.5	0.76 (0.61–0.94)	0.01
Heart-failure hospitalization	12.0	18.4	0.58 (0.47–0.70)	<0.001
Hospitalization for hyperkalemia	0.3	0.2	1.15 (0.25–5.31)	0.85

Insuffisance rénale ⟺ Diabète

LCZ diabétiques

Diabetic	LCZ	Enalapril
No	2736	2756
Yes	1451	1456

Critère primaire  0,405

Mortalité CV  0,05

Vu sur Akenini.com