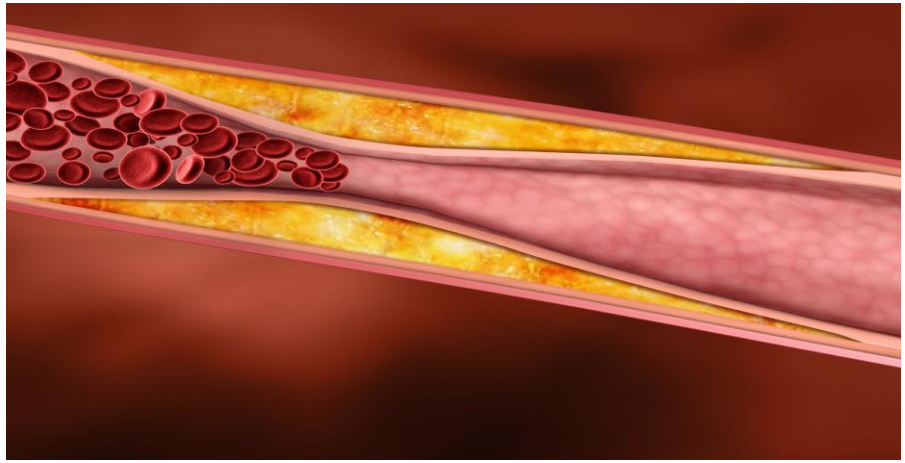
חידושים ו"פנינו לאן?"
טיפול תרופתי בסוכרת והיפרליפידמיה בנשים

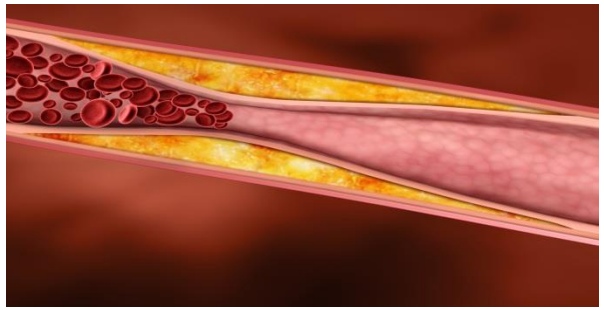
ד"ר עידית דוברצקי מרי
טיפול נמרץ לב, בני ציון
טכניון הפקולטה לרפואה חיפה



Pathology of Human Coronary and Carotid Artery Atherosclerosis and Vascular Calcification in Diabetes Mellitus

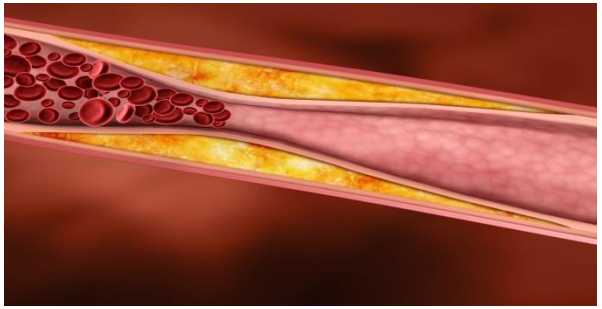
Kazuyuki Yahagi, Frank D. Kolodgie, Christoph Lutter, Hiroyoshi Mori, Maria E. Romero, Aloke V. Finn, Renu Virmani

- Pathological findings in Sudden coronary death
- Coronary lesion morphology
- Healed plaque rupture
- Positive remodeling
- Calcification and coronary artery risk / Vascular calcification
- Factor promoting DM plaque calcification



Healed plaque rupture

- Significantly higher incidence of asymptomatic ischemic disease
- 39% of sudden coronary death shows > 3 HPR per heart vs 13% in on DM subjects



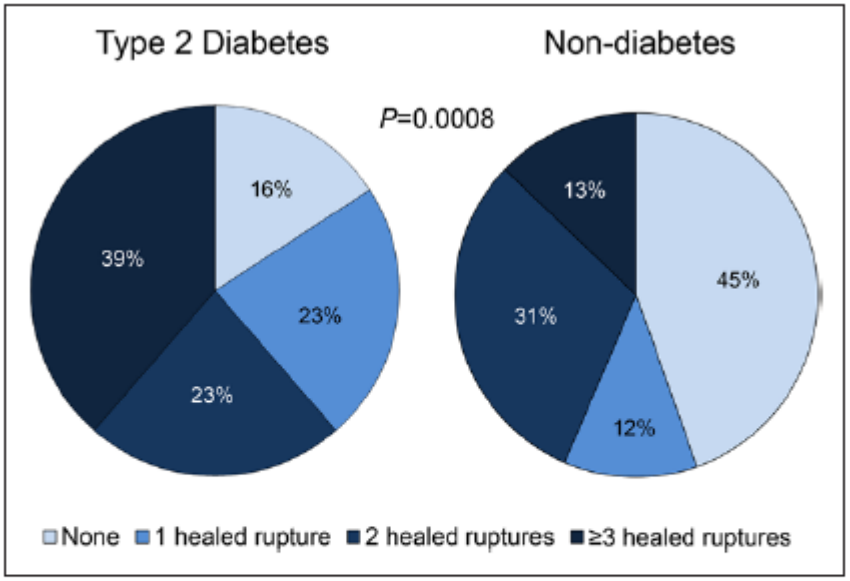
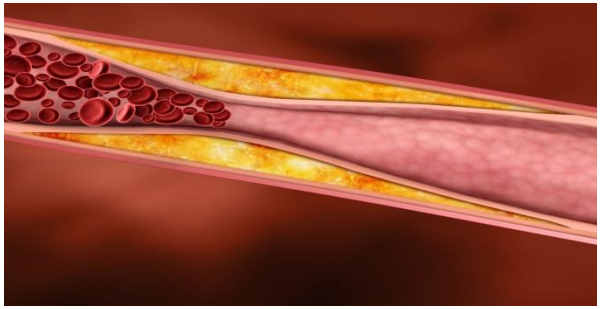


Figure 2. The pie charts reflect the percentage of healed ruptures (HPR) per heart relative to diabetic status at autopsy. Type 2 diabetes mellitus had higher numbers of HPRs compared with nondiabetics (P=0.0008). The data constitute a reanalysis of 142 sudden coronary death cases, published in Burke et al[14] and stratified by with or without diabetes mellitus.

Calcification and coronary artery risk / Vascular calcification

- Calcification both intima and media
- Medial calcification rare in coronary



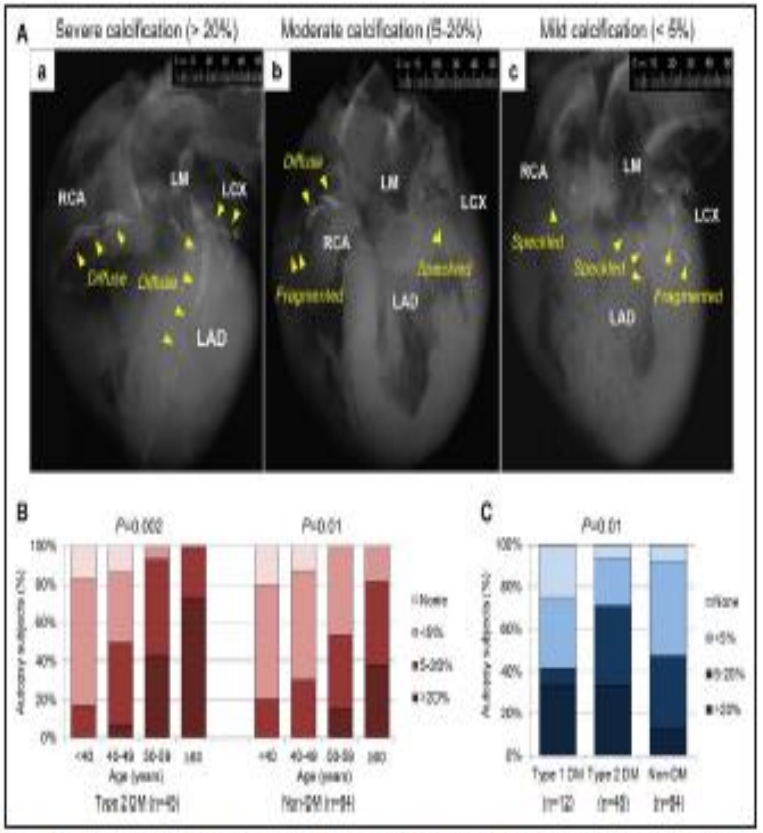
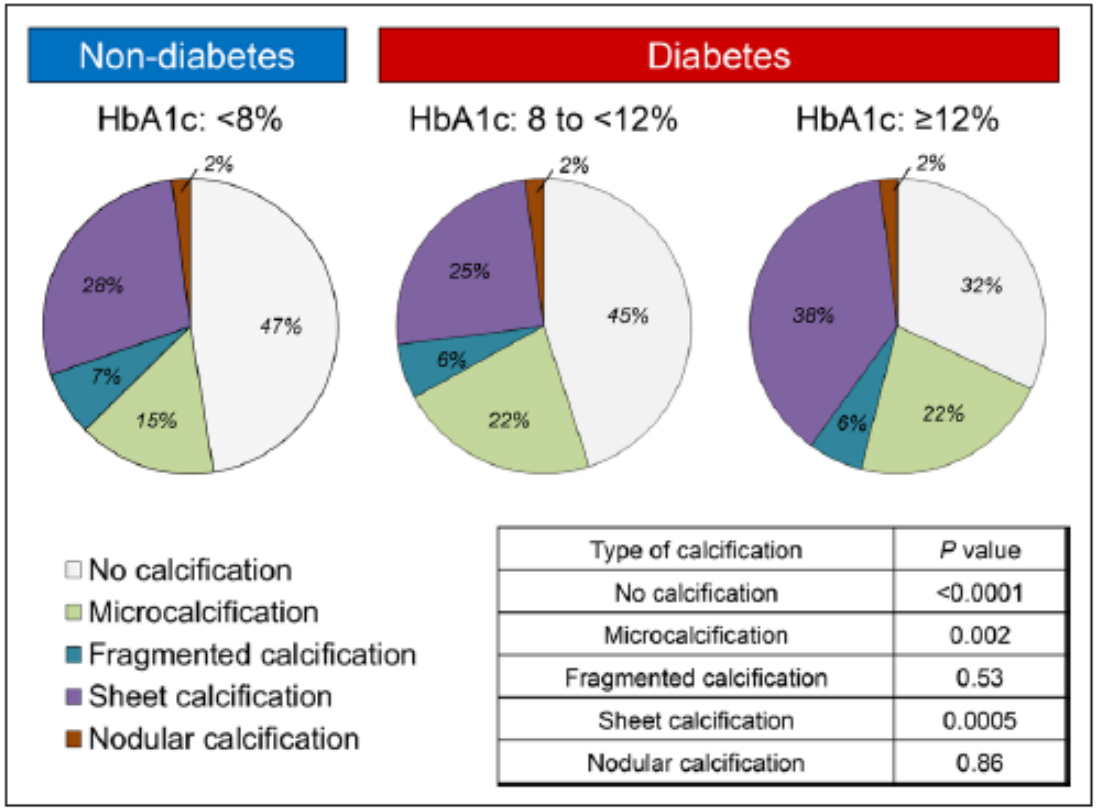


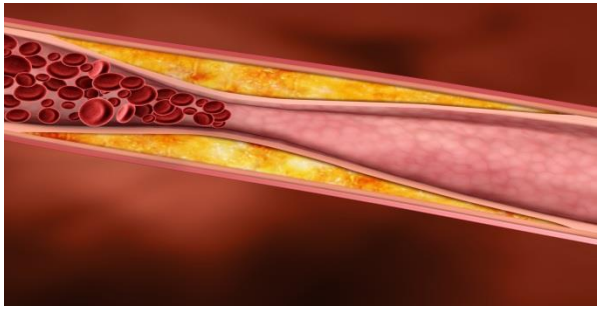
Figure 3. Coronary artery calcification in sudden coronary death evaluated by postmortem radiography. **A**, Representative postmortem radiographs showing various patterns of calcification. The severity of calcification was assessed based on the percentage of calcification area: (a) severe artery calcification (>20%), (b) moderate calcification (5%–20%), and (c) mild calcification (<5%). Arrows indicate type of calcification (speckled [<2 mm in length], fragmented [2–5 mm], or diffuse [>5 mm] calcification]. **B**, Percentage of total calcified area, divided into mild, moderate, and severe in sudden coronary death patients with type 2 diabetes mellitus (DM) and non-DM stratified by decade. **C**, Percentage of total calcified area in sudden coronary death comparing type 1 DM, type 2 DM, and non-DM. LAD indicates left anterior descending; LCX, left circumflex; LM, left main; and RCA, right coronary artery.

Calcification and coronary artery risk / Vascular calcification

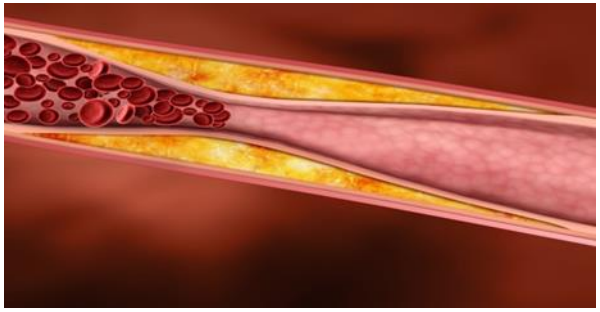


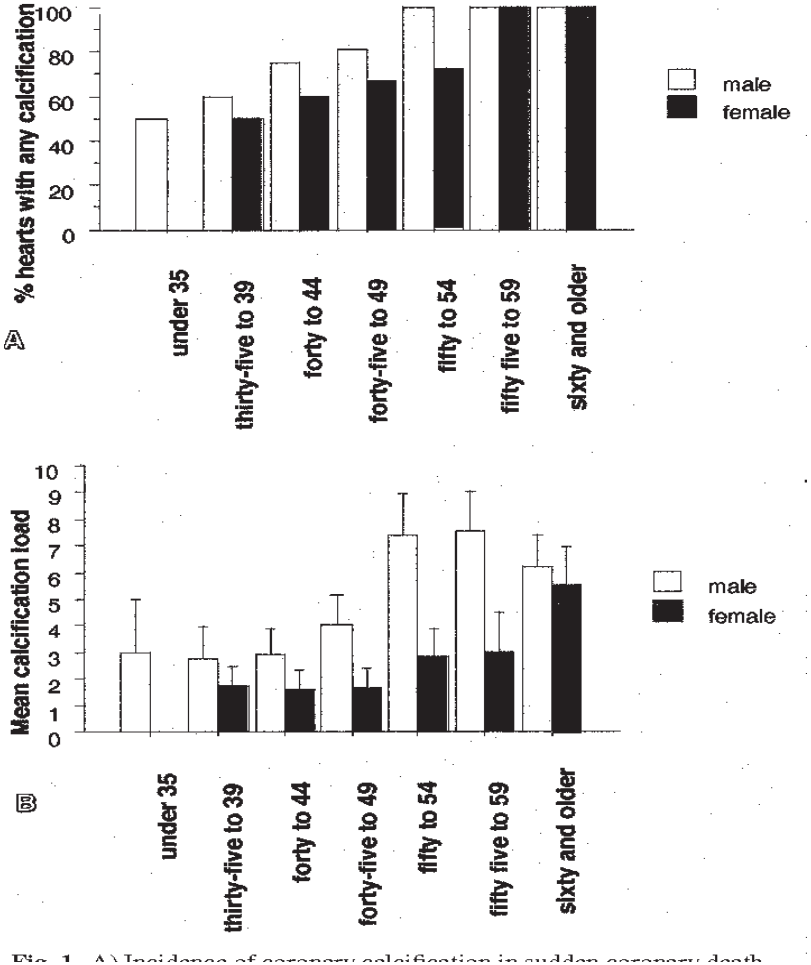
Type of calcification	*P* value
No calcification	<0.0001
Microcalcification	0.002
Fragmented calcification	0.53
Sheet calcification	0.0005
Nodular calcification	0.86

Figure 4. Percentage of sudden deaths based on coronary artery calcification type (none, micro, fragmented, sheet, and nodular), stratified by HbA1c level (<8%) nondiabetics and diabetic (8% to <12% and ≥12%). Histological sections (1630; <8%, n=776 sections; 8% to <12%, n=548; and ≥12%, n=306) from 57 patients with stable coronary artery disease were examined. Note the declining shift in the number of lesions without calcification and significant reciprocal increase sheet calcification with escalating HbA1C levels.

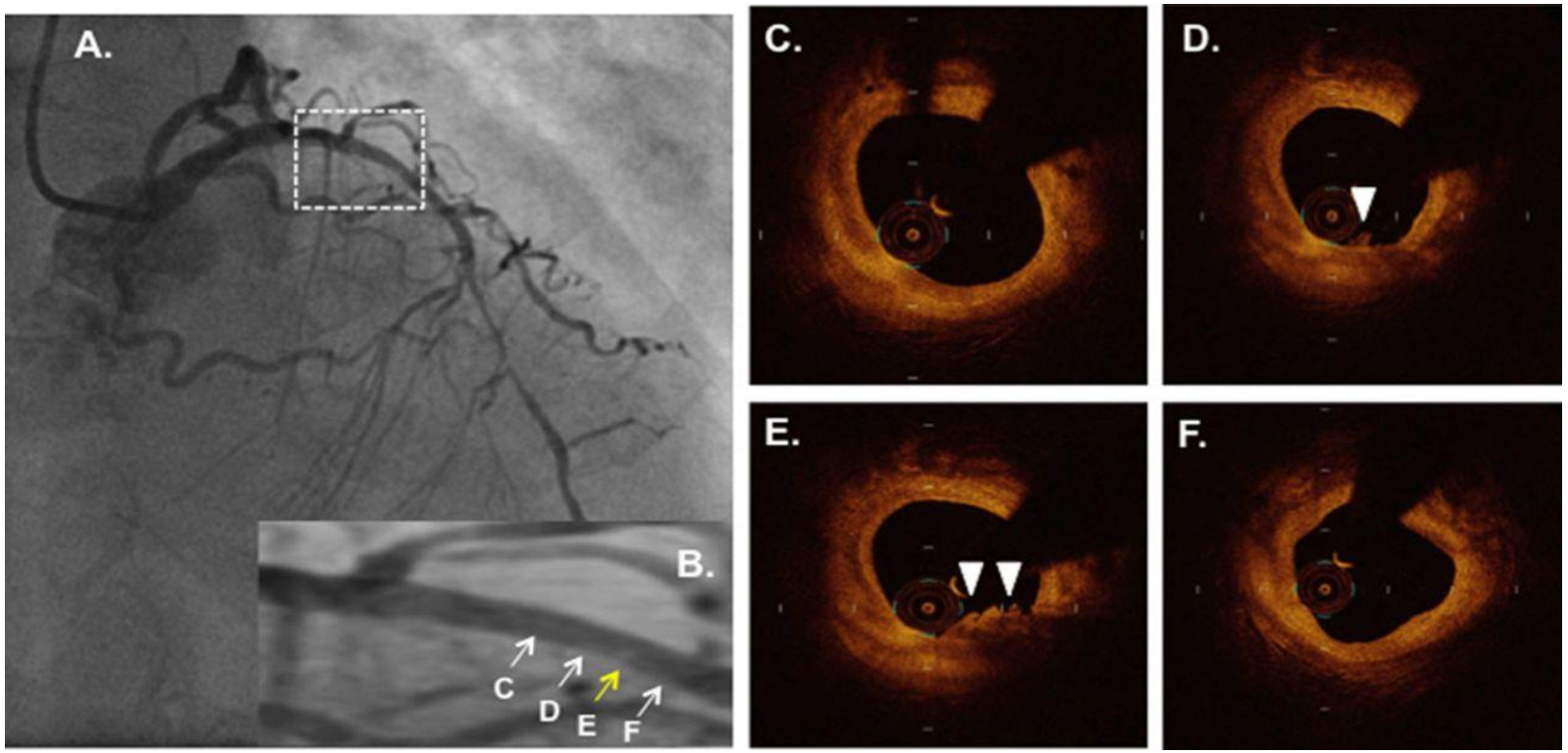


Insights Into Coronary Plaque Microstructure Differences Between Women and Men





Sex Differences in Nonculprit Coronary Plaque Microstructures on Frequency-Domain Optical Coherence Tomography in Acute Coronary Syndromes and Stable Coronary Artery Disease



FD-OCT images in women. A 52-y-old woman presented stable coronary artery disease. Coronary angiography demonstrated a mild (nonculprit lesion) and a tight stenosis (culprit lesions) at proximal and mid LAD , respectively (A). Haziness within the vessel (yellow arrow) was observed (B). FD-OCT imaging visualized fibrous plaque (C–F). D and E, An irregular lumen surface with attached mural thrombus, indicating plaque erosion.

Circulation: Cardiovascular Imaging. 2016

DIABETES

Sex and Gender Differences in Risk, Pathophysiology and Complications of Type 2 Diabetes Mellitus

Alexandra Kautzky-Willer, Jürgen Harreiter, and Giovanni Pacini

Gender Medicine Unit (A.K.-W., J.H.), Division of Endocrinology and Metabolism, Department of Internal Medicine III, Medical University of Vienna, 1090 Vienna, Austria; and Metabolic Unit (G.P.), Institute of Neuroscience, National Research Council, 35127 Padua, Italy

Figure 3.

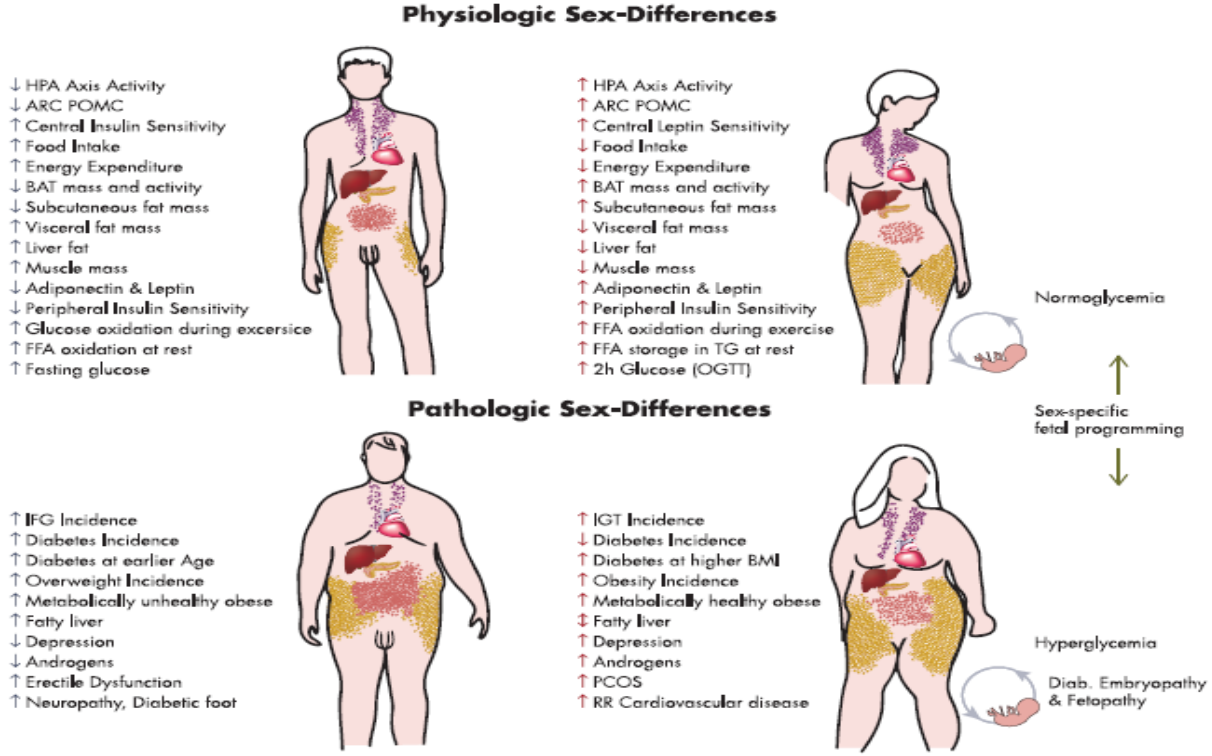
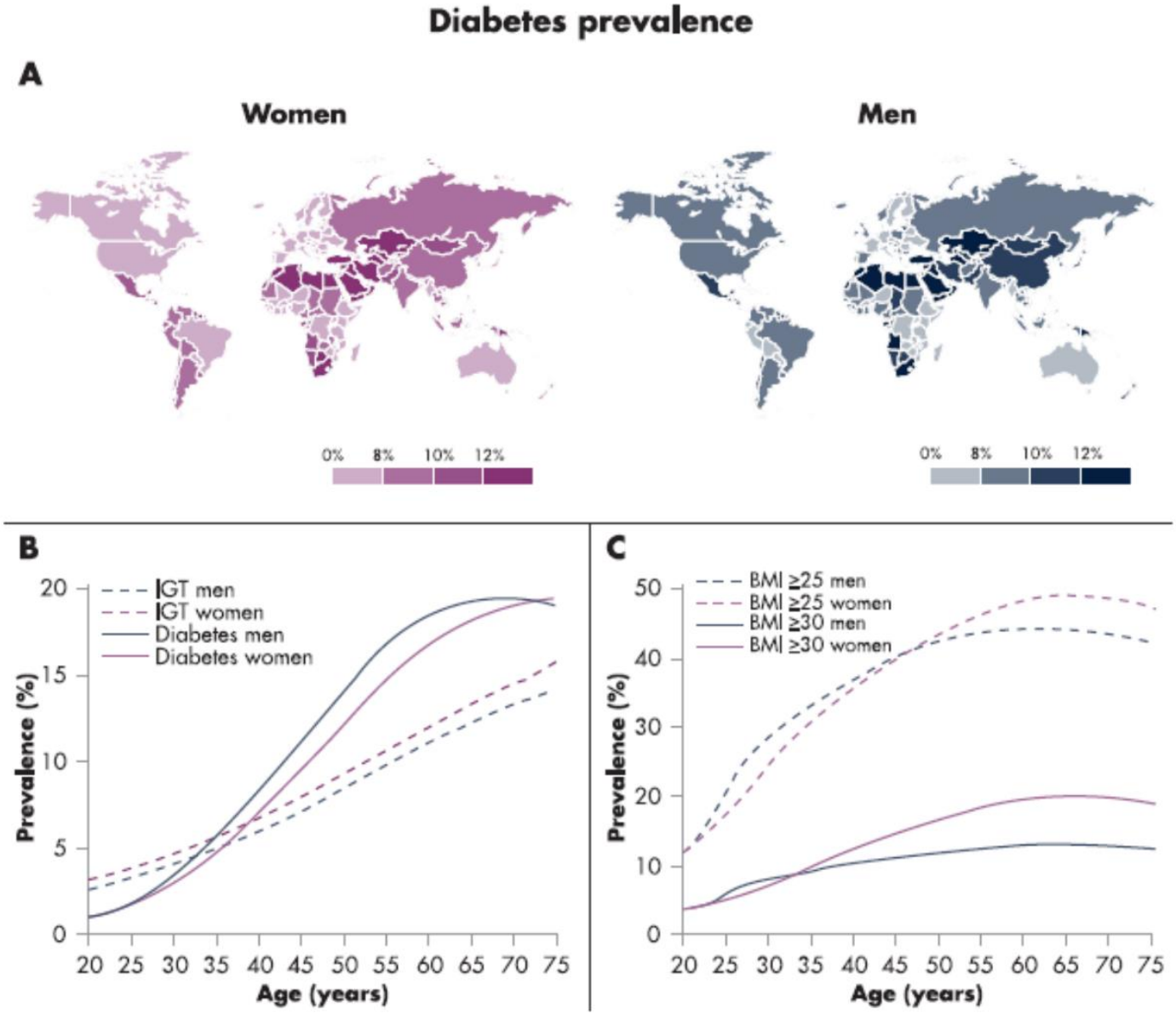


Figure 3. Overview of physiological and pathological sex differences in metabolism and energy homeostasis in men (left) and women (right). Blue arrows indicate higher or lower levels or impact in men compared with women. Red arrows indicate higher or lower levels or impact in women compared with men. Fat mass: red, SAT; orange, VAT; purple, BAT. ARC POMC, arcuate nucleus POMC; FFA, free fatty acid; RR, relative risk. These facts are described in more detail in the main text, eg, in the sections II and V, respectively.

Figure 2.


Diabetes prevalence
A
Women
Men
0% 8% 10% 12%
0% 8% 10% 12%
B
IGT men
IGT women
Diabetes men
Diabetes women
Prevalence (%)
Age (years)
C
BMI ≥25 men
BMI ≥25 women
BMI ≥30 men
BMI ≥30 women
Prevalence (%)
Age (years)

RESEARCH ARTICLE

Women are less likely than men to achieve optimal glycemic control after 1 year of treatment: A multi-level analysis of a Korean primary care cohort

Seung-Ah Choe[1,2], Joo Yeong Kim[3], Young Sun Ro[4], Sung-Il Cho[5]*

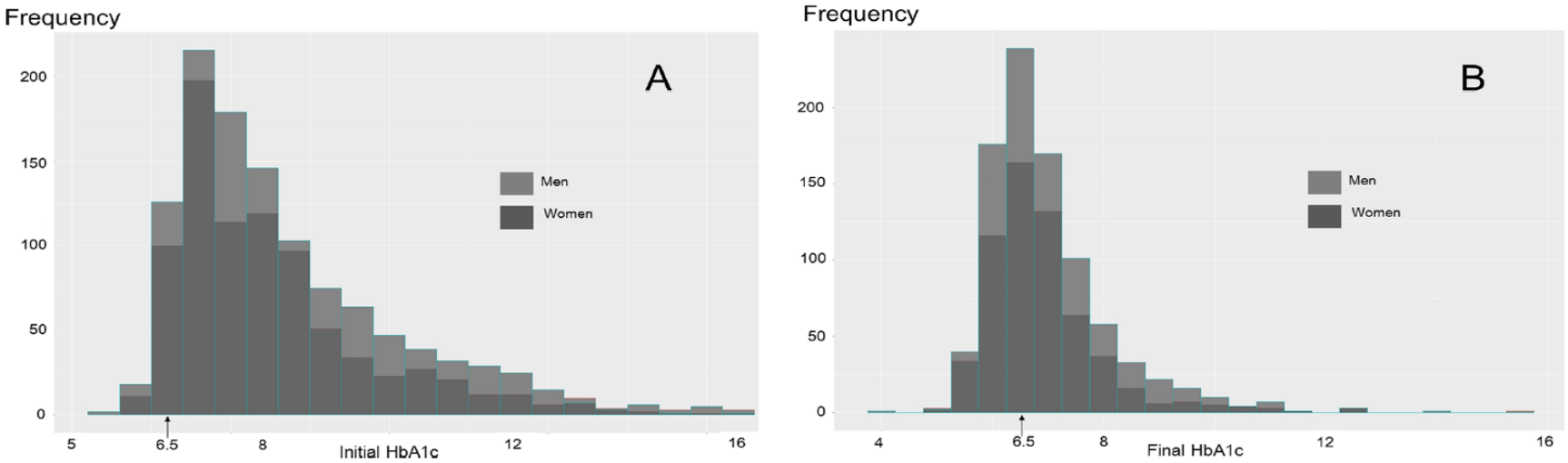


Fig 1. Hemoglobin A1c (HbA1c) levels of women and men diagnosed with type-2 diabetes at primary care clinics (N = 2,253); (A) Initial HbA1c; and (B) Final HbA1c after 1 year.

Conclusions

In conclusion, among newly diagnosed type-2 diabetic patients in participating primary clinics, female patients were less likely to achieve the target HbA1c level after 1 year of diabetes management. For more effective diabetic management, a sex-specific management protocol that considers the differences in clinical features between women and men is needed.

International Journal of CARDIOLOGY

A systematic review and meta-regression of temporal trends in the excess mortality associated with diabetes mellitus after myocardial infarction

PubMed database for studies reporting mortality data according to diabetic status in patients hospitalized for MI or acute coronary syndromes (ACS).
We included 139 studies/cohorts for analysis (**432,066 diabetic patients and 1,182,108 nondiabetic patients).**

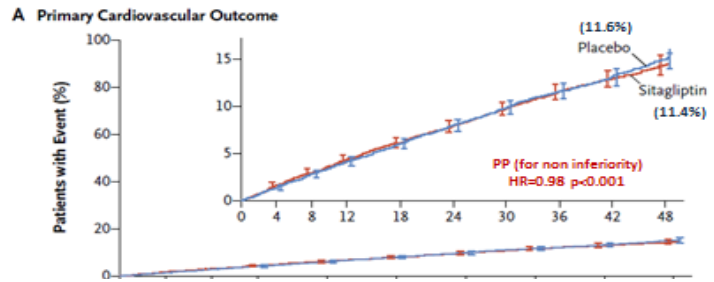
Conclusions

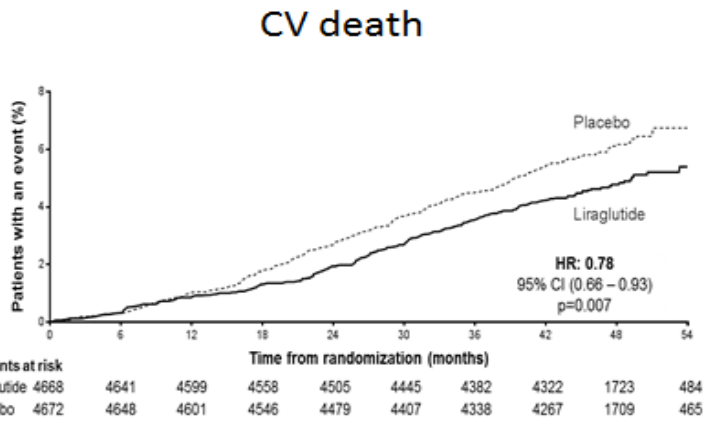
We found no evidence for temporal changes in the incremental mortality risk associated with DM in the setting of MI. The improvements in management of MI patients during the last decades have not been associated with a reduction of the gap between diabetic and non-diabetic patients.

August 15, 2016Volume 217, Pages 109–121

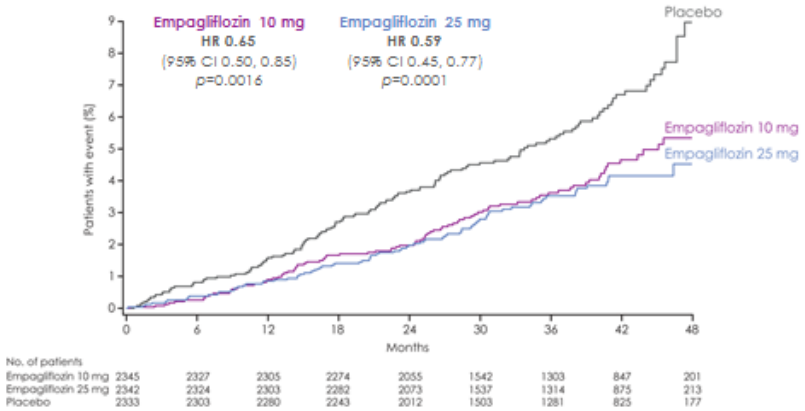
Case presentation – DM Chronic phase

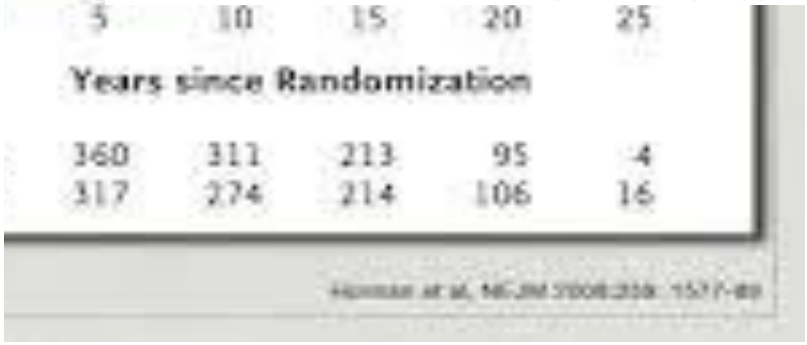
תוצאות: לא היה הבדל בשכיחות
*Primary End-Point אירועי ה-





CV death





Cumulative incidence function. HR, hazard ratio

women - under-represented in CV outcome trials, resulting in less certainty about the impact of CV prevention therapies across the sexes

TRIALS	PERCENTAGE %	AGE		

Table: Association of Sex and Endpoints

Endpoint	Total events (W)	Events per 100 pt-yrs (W)	Total events (M)	Events per 100 pt-yrs (M)	HR (95% CI) for female v. male	Adjusted HR (95% CI) for female v. male	Adjusted p
CV death, MI, Stroke, o Hospitalization for UA						, 0.83)	<0.0001
CV death, MI, Stroke						, 0.81)	<0.0001
CV death						, 0.81)	0.0003
Myocardial infarction						, 0.91)	0.0081
Stroke						, 0.92)	0.0151
Hospitalization for UA	58	0.47	187	0.62	0.78 (0.58, 1.05)	0.87 (0.56, 1.33)	0.5159
All Cause Death	279	2.17	805	2.58	0.80 (0.69, 0.91)	0.68 (0.56, 0.82)	<0.0001
Hospitalization for HF	115	0.93	342	1.14	0.83 (0.67, 1.03)	0.84 (0.64, 1.12)	0.2414

Cox proportional hazards regression models are used. Data are censored at the last day the patient is known to be free of the event. Models are repeated with adjustment for duration of diabetes and baseline variables determined to differ.

W = women; M = men; MI = myocardial infarction; UA = unstable angina; HF = heart failure

These data suggest that the cardioprotective effect of female sex extends to populations with T2DM

LIPIDS

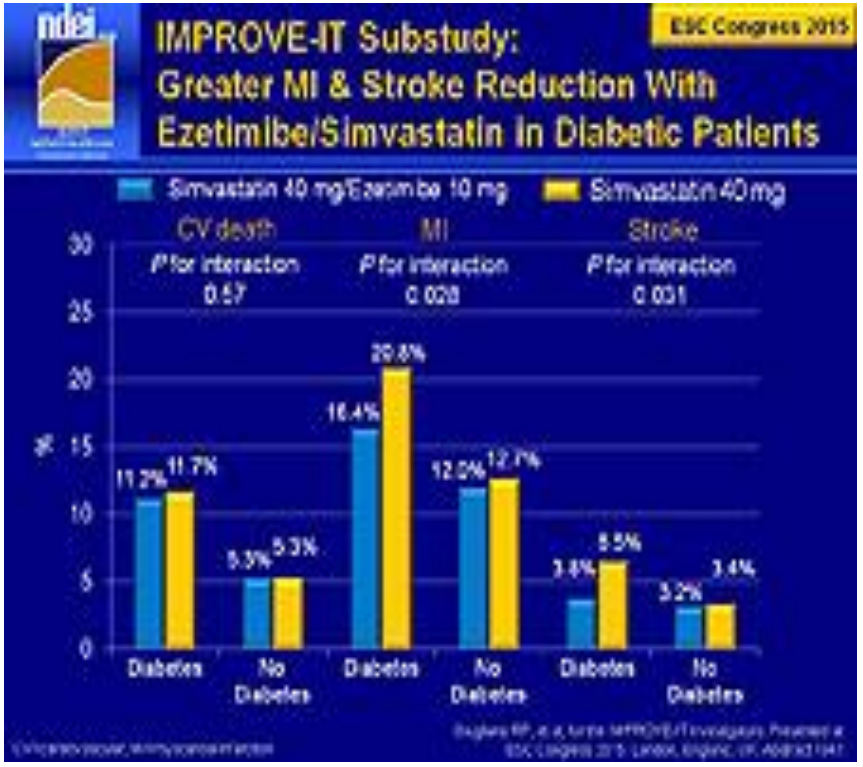
women - under-represented in CV outcome trials, resulting in less certainty about the impact of CV prevention therapies across the sexes

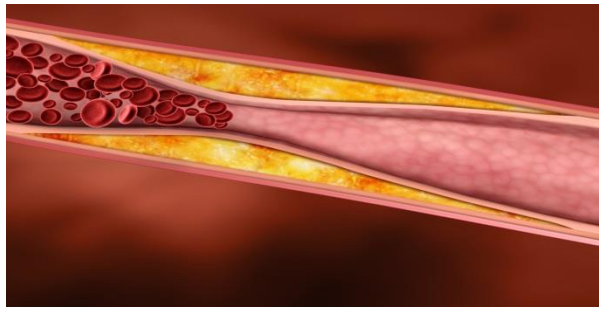
TRIAL	PERCENTAGE %	AGE	DIABETES %
IMPROVE IT	25	63	FEMALE -32 MALE-26
FOURIER	25	63	34
ODYSSEY	24	58	29

IMPROVE IT – DM

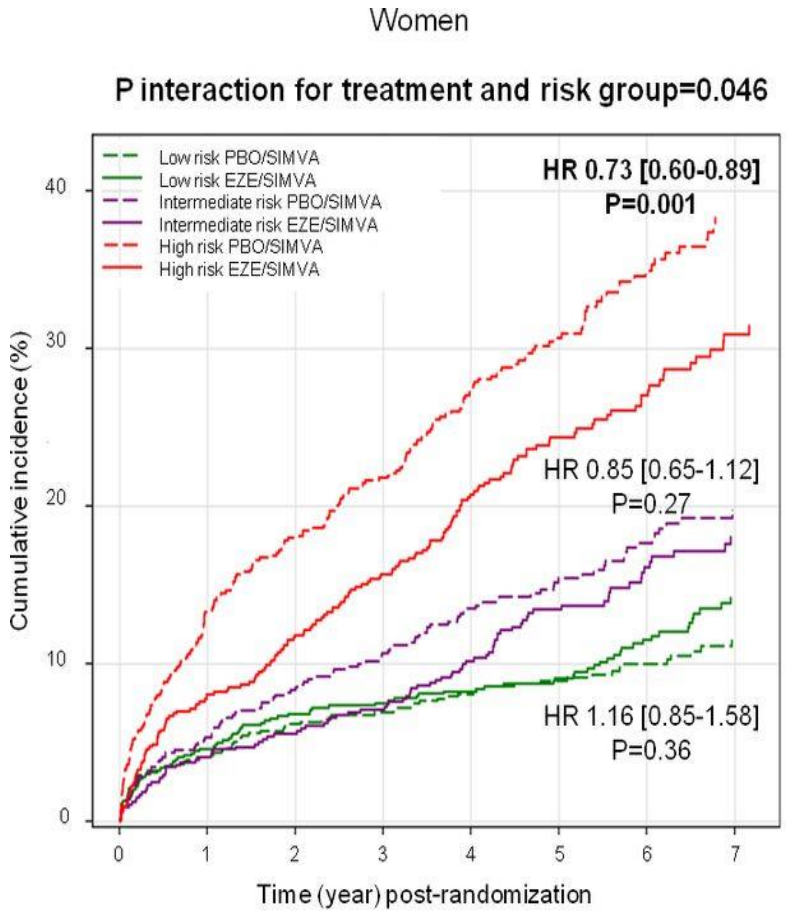
Ezetimibe/simvastatin reduced the primary endpoint rate by 14% in diabetic subjects
The primary composite endpoint occurred in 40.0% of diabetic subjects who were assigned simvastatin/ezetimibe (n=2,459) compared with 45.5% of those treated with simvastatin alone (n=2,474)—a reduction of 14% (HR=0.86; *P*=0.023).

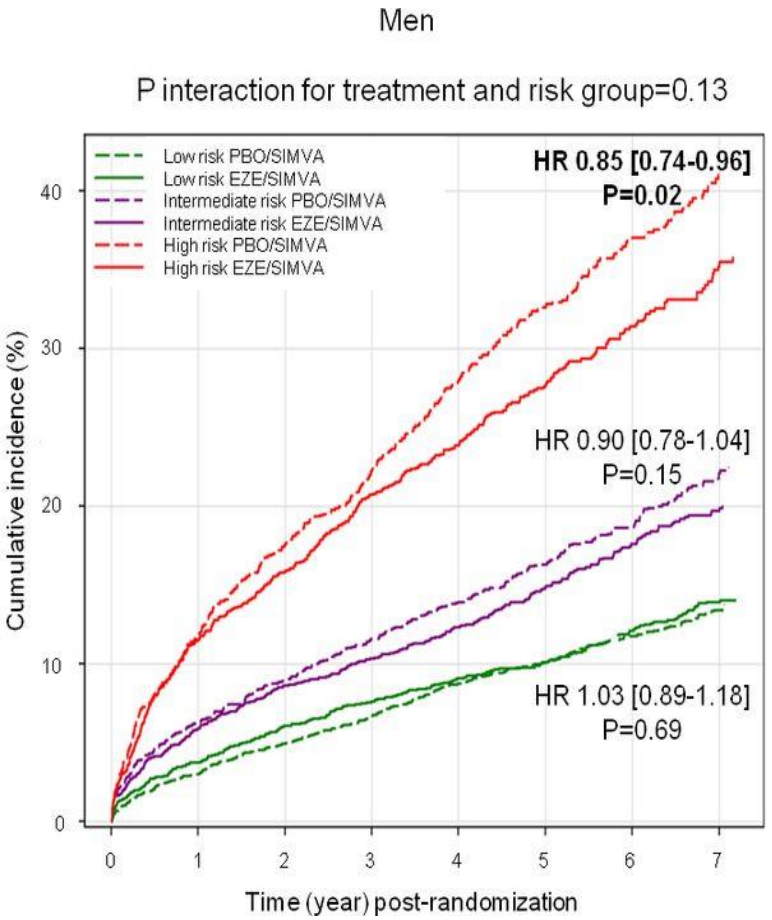
Conversely, no difference was seen in the rate of
the primary endpoint for nondiabetic subjects treated with ezetimibe vs placebo: 30.2% vs 30.8%





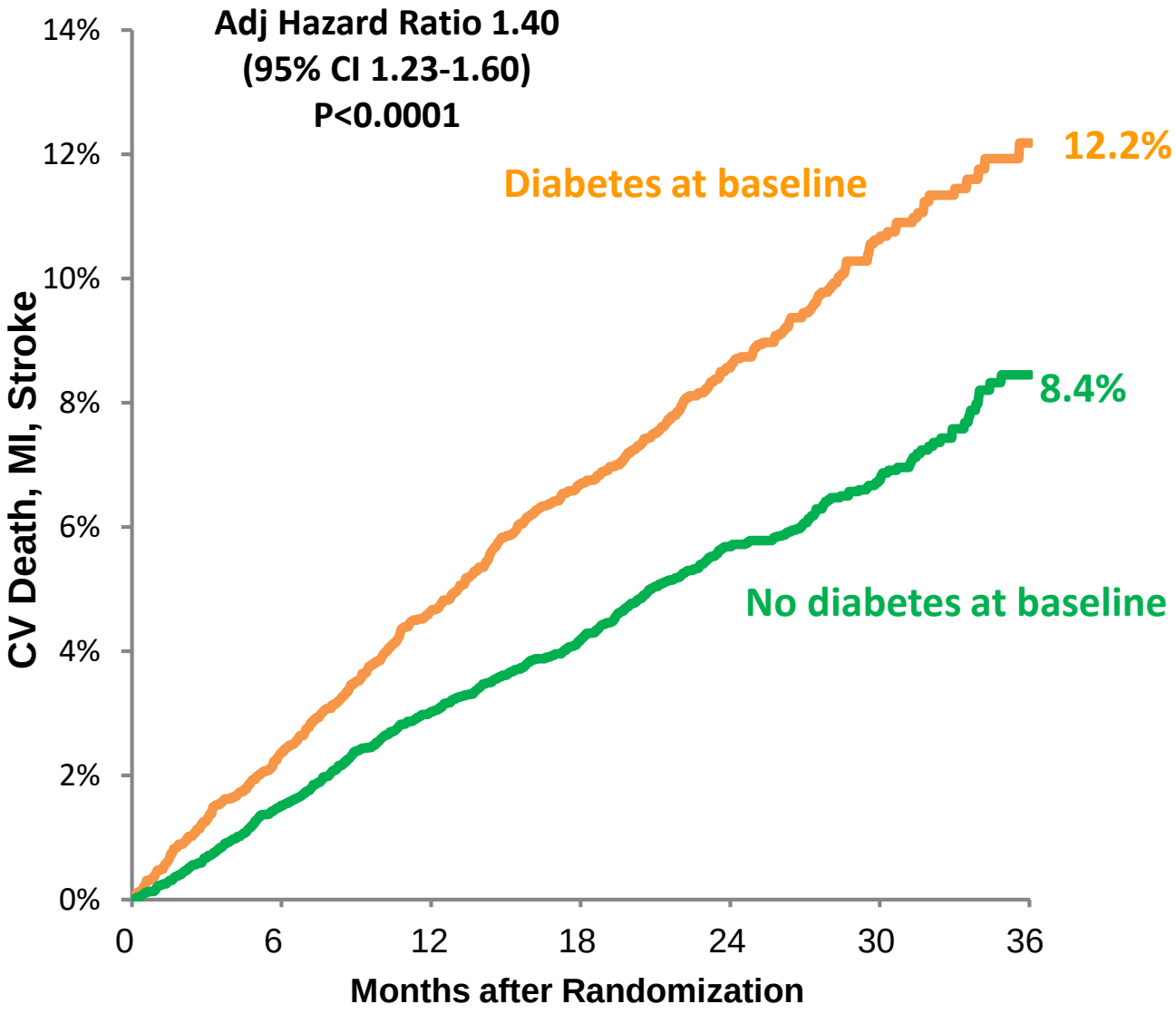
IMPROVE IT


Women
P interaction for treatment and risk group=0.046
Low risk PBO/SIMVA
Low risk EZE/SIMVA
Intermediate risk PBO/SIMVA
Intermediate risk EZE/SIMVA
High risk PBO/SIMVA
High risk EZE/SIMVA
HR 0.73 [0.60-0.89]
P=0.001
HR 0.85 [0.65-1.12]
P=0.27
HR 1.16 [0.85-1.58]
P=0.36
Cumulative incidence (%)
0
10
20
30
40
0
1
2
3
4
5
6
7
Time (year) post-randomization

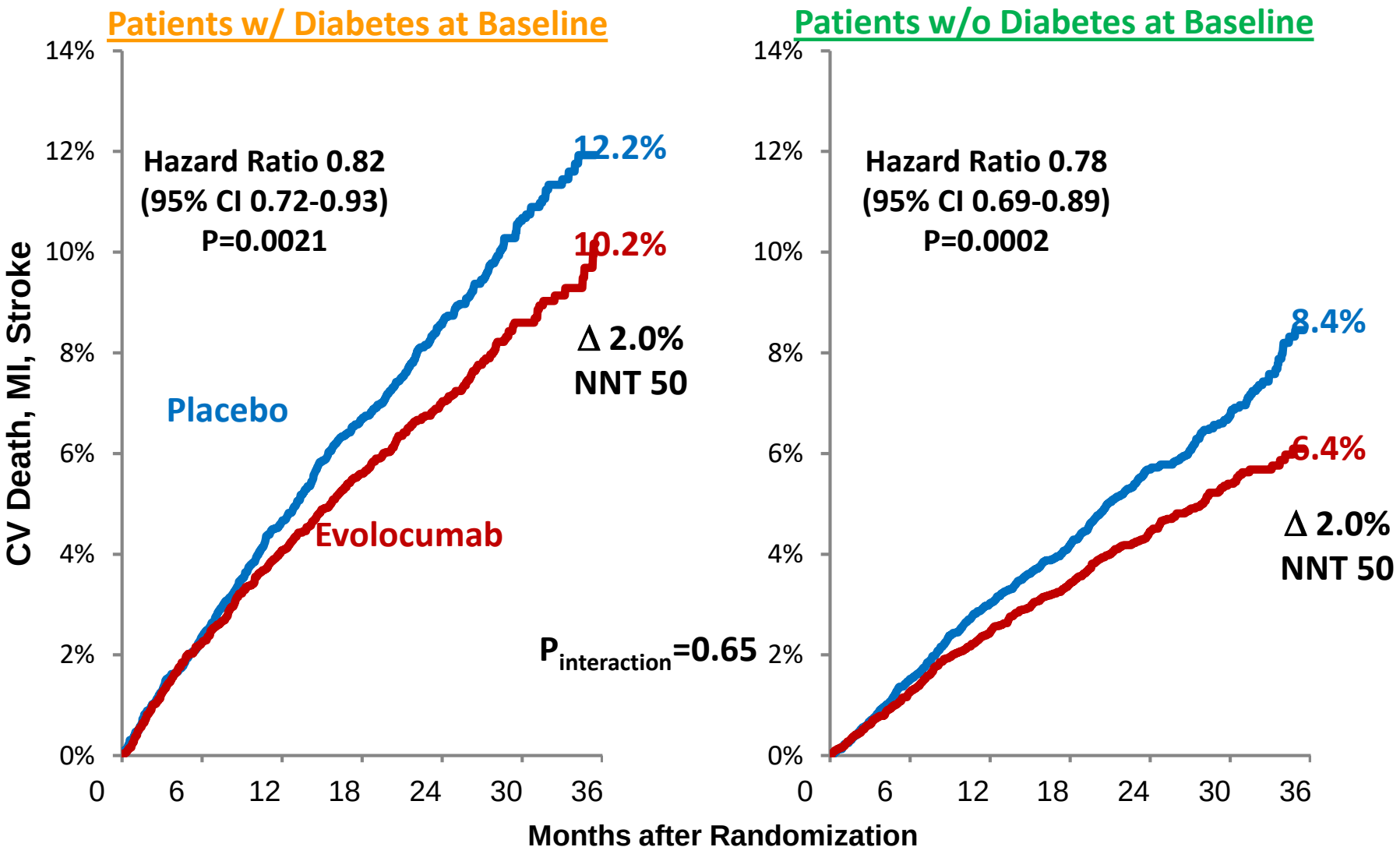

Men
P interaction for treatment and risk group=0.13
Low risk PBO/SIMVA
Low risk EZE/SIMVA
Intermediate risk PBO/SIMVA
Intermediate risk EZE/SIMVA
High risk PBO/SIMVA
High risk EZE/SIMVA
HR 0.85 [0.74-0.96]
P=0.02
HR 0.90 [0.78-1.04]
P=0.15
HR 1.03 [0.89-1.18]
P=0.69
Cumulative incidence (%)
0
10
20
30
40
0
1
2
3
4
5
6
7
Time (year) post-randomization

LIPIDS PCSK9 ab

FOURIER – DM (MI,CVA ,DEATH)



FOURIER – DM (MI,CVA ,DEATH)



ODYSSEY

ACC.18

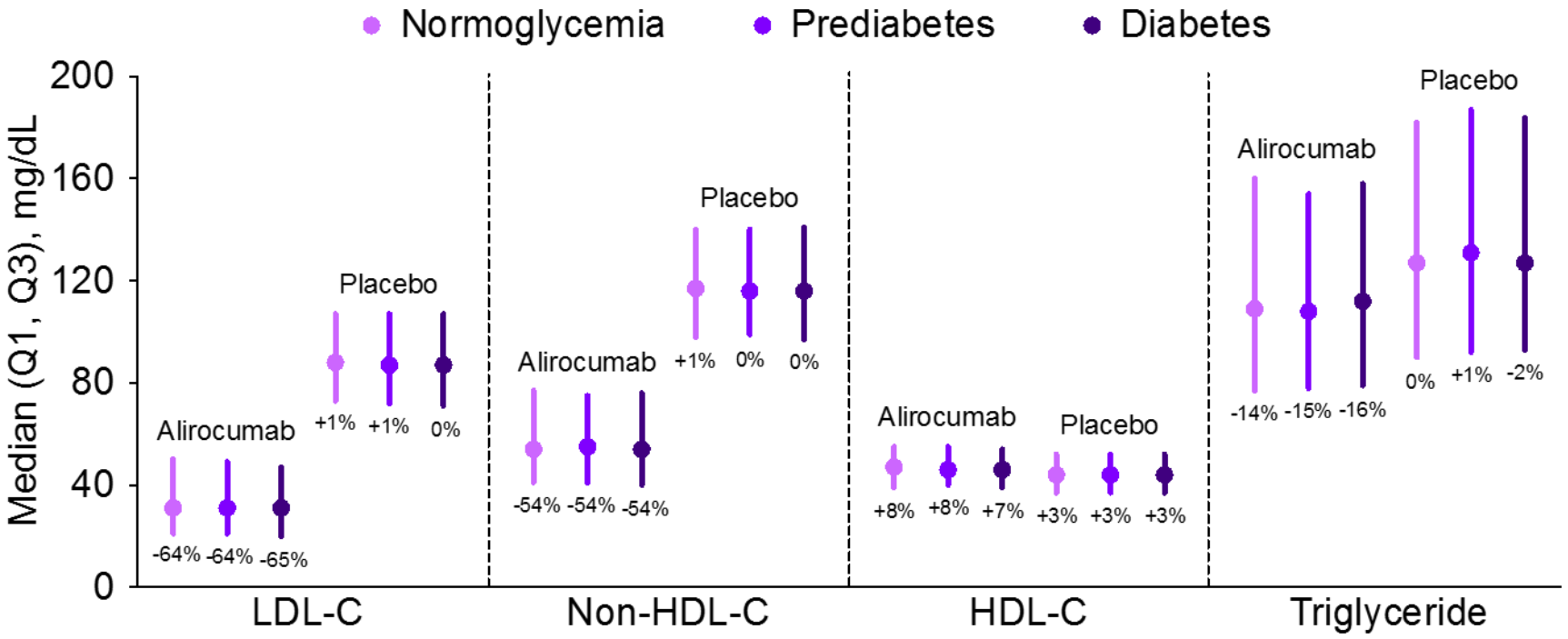
Efficacy: Subgroup with Baseline LDL-C ≥100 mg/dL (Median Baseline LDL-C 118 mg/dL)

Endpoint, n (%)	Alirocumab (N=2814)	Placebo (N=2815)	Absolute risk reduction (%)	HR (95% CI)
MACE	324 (11.5)	420 (14.9)	3.4	**0.76** (0.65, 0.87)
CHD death	69 (2.5)	96 (3.4)	1.0	**0.72** (0.53, 0.98)
CV death	81 (2.9)	117 (4.2)	1.3	**0.69** (0.52, 0.92)
All-cause death	114 (4.1)	161 (5.7)	1.7	**0.71** (0.56, 0.90)

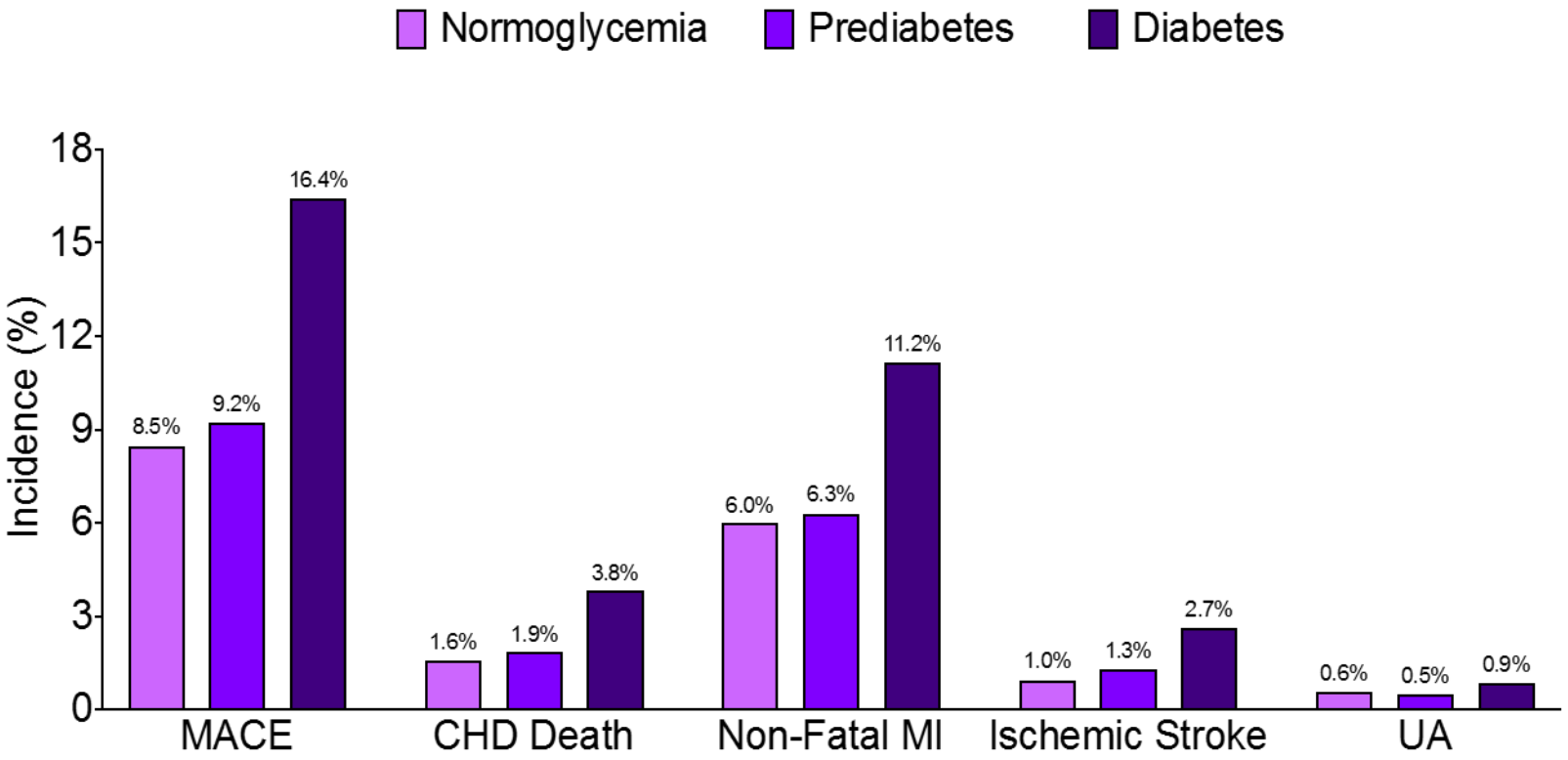
HIGH RISK

ODYSSEY OUTCOMES

ODYSSEY - DM


Normoglycemia
Prediabetes
Diabetes
Median (Q1, Q3), mg/dL
200
160
120
80
40
0
Alirocumab
Placebo
-64% -64% -65%
+1% +1% 0%
Alirocumab
Placebo
-54% -54% -54%
+1% 0% 0%
Alirocumab
Placebo
+8% +8% +7%
+3% +3% +3%
Alirocumab
Placebo
-14% -15% -16%
0% +1% -2%
LDL-C
Non-HDL-C
HDL-C
Triglyceride

ODYSSEY - DM

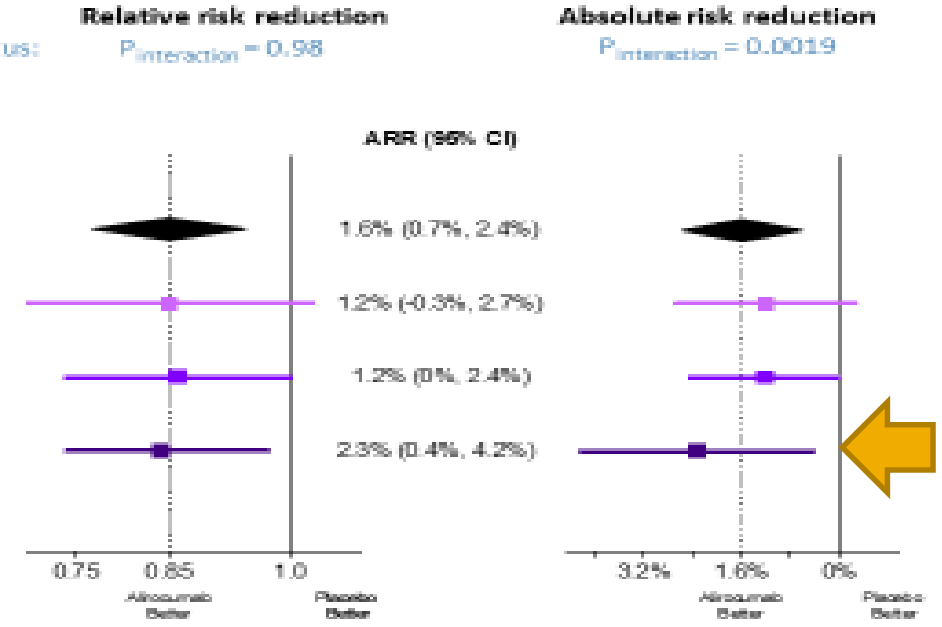

Normoglycemia
Prediabetes
Diabetes
Incidence (%)
18
15
12
9
6
3
0
8.5%
9.2%
16.4%
1.6%
1.9%
3.8%
6.0%
6.3%
11.2%
1.0%
1.3%
2.7%
0.6%
0.5%
0.9%
MACE
CHD Death
Non-Fatal MI
Ischemic Stroke
UA

ODYSSEY - DM

Relative and Absolute Risk Reduction with Alirocumab By Glucometabolic Status

Treatment × baseline glucometabolic status: $P_{interaction} = 0.98$

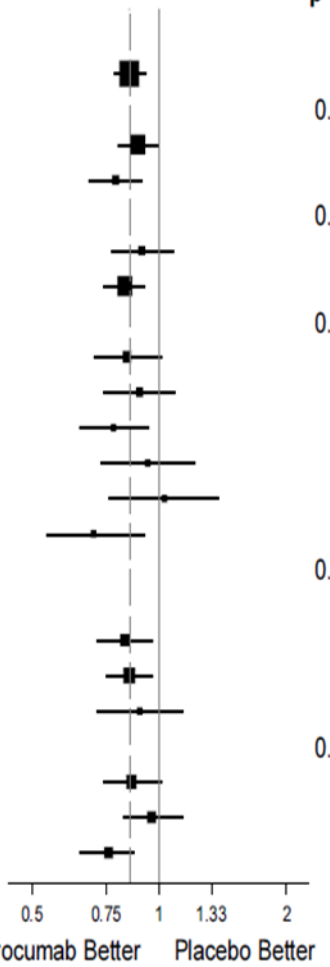
Subgroup	MACE Incidence Alirocumab n/N (%)	MACE Incidence Placebo n/N (%)	HR (95% CI)	ARR (96% CI)
Overall	903/9462 (9.5)	1052/9462 (11.1)	0.85 (0.78, 0.93)	1.6% (0.7%, 2.4%)
Normoglycemia	192/2639 (7.3)	220/2595 (8.5)	0.85 (0.70, 1.03)	1.2% (-0.3%, 2.7%)
Prediabetes	331/4130 (8.0)	380/4116 (9.2)	0.86 (0.74, 1.00)	1.2% (0%, 2.4%)
Diabetes	380/2693 (14.1)	452/2751 (16.4)	0.84 (0.74, 0.97)	2.3% (0.4%, 4.2%)



Median (Q1, Q3) follow-up: 2.8 (2.3, 3.4) years

ODYSSEY - DM

Subgroup	Patients	Incidence (%) Alirocumab	Placebo	HR (95% CI)	p-value*
Overall	18924	9.5	11.1	0.85 (0.78, 0.93)	
Age					0.19
< 65 Yr	13840	8.5	9.5	0.89 (0.80, 0.99)	
≥ 65 Yr	5084	12.4	15.5	0.79 (0.68, 0.91)	
Sex					0.35
Female	4762	10.7	11.8	0.91 (0.77, 1.08)	
Male	14162	9.2	10.9	0.83 (0.74, 0.92)	
Region					0.40
Eastern Europe	5437	7.9	9.3	0.84 (0.70, 1.01)	
Western Europe	4175	9.1	10.0	0.90 (0.74, 1.09)	
North America	2871	13.7	17.1	0.78 (0.65, 0.94)	
South America	2588	9.1	9.7	0.94 (0.73, 1.21)	
Asia	2293	7.7	7.6	1.03 (0.76, 1.38)	
Rest of World	1560	12.2	16.7	0.70 (0.54, 0.92)	
Time from Index Event to Randomization					0.85
<2 Months	6178	10.3	12.3	0.83 (0.71, 0.96)	
2 - <6 Months	9518	9.6	11.1	0.85 (0.75, 0.96)	
≥6 Months	3228	8.0	8.7	0.90 (0.71, 1.14)	
LDL (mg/dL)					0.09
<80	7164	8.3	9.5	0.86 (0.74, 1.01)	
80 - <100	6128	9.2	9.5	0.96 (0.82, 1.14)	
≥100	5629	11.5	14.9	0.76 (0.65, 0.87)	



* p-values from tests of interaction between treatment and subgroups.

לסיכום

- חולי סוכרת ובעיקר מסוג 2 מציגים אתגר גדול בטיפול נוכח טרשת עורקים מואצת ושילוב גורמי סיכון מהותיים נוספים במקביל
- מראה הטרשת התנהגותה ברקמה כבר מגיל צעיר טרום קליני שונה לעומת מטופלים לא סוכרתיים
- נשים סוכרתיות נמצאת בסיכון להתפתחות אירועים CV כמעט זהה לגברים בני גילם
- מחקרי CV OUTCOME אחרונים בסוכרת וליפידים מדגימים יכולת התמודדות עם הבעיה תוך הפחתה בתחלואה ואף בתמותה באוכלוסיות בסיכון גבוה מאד ללא הבדל מובהק בין המגדרים .

High Resolution Longitudinal Immune Profiling Reveals the Dynamics of Healthy Immune-Aging and its Relation to Cardiovascular Risk

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135 healthy individuals of different ages sampled longitudinally over a nine-year period.
High inter-individual variability in the rates of change of cellular frequencies that correlate with baseline values

IMM-AGE score increases predictive power of a future cardiovascular event beyond well-established risk factors in the Framingham Heart Study.

שבת שלום