# *Running the Race for CAD Protection in Diabetes: Status 2019*
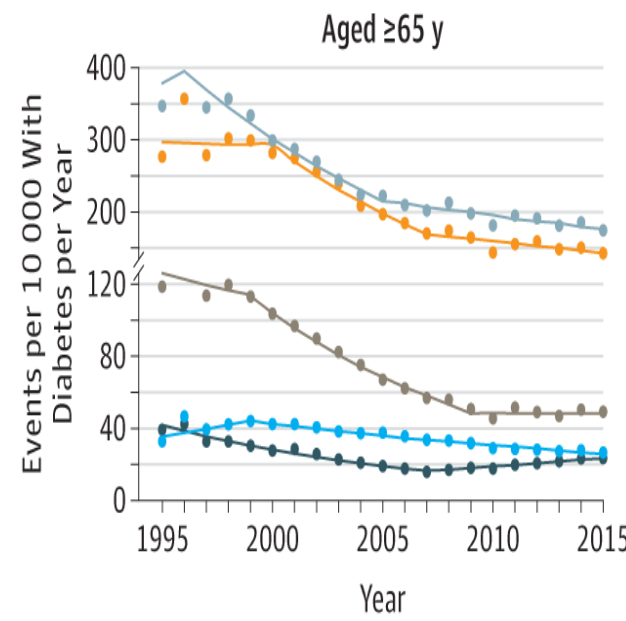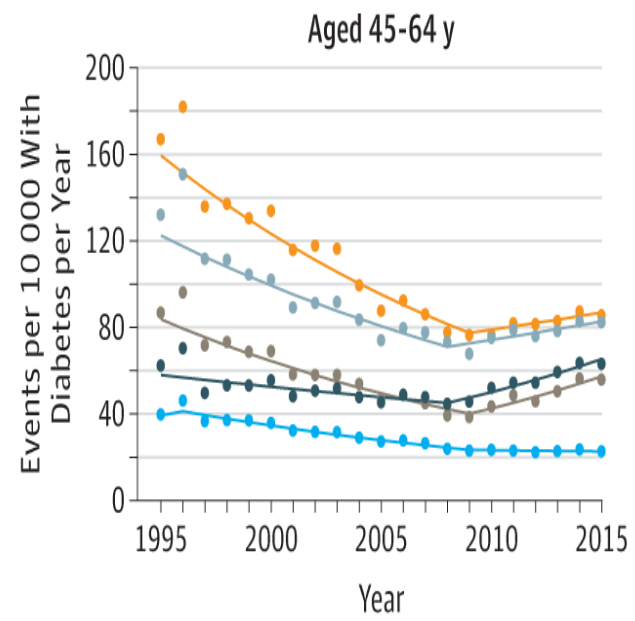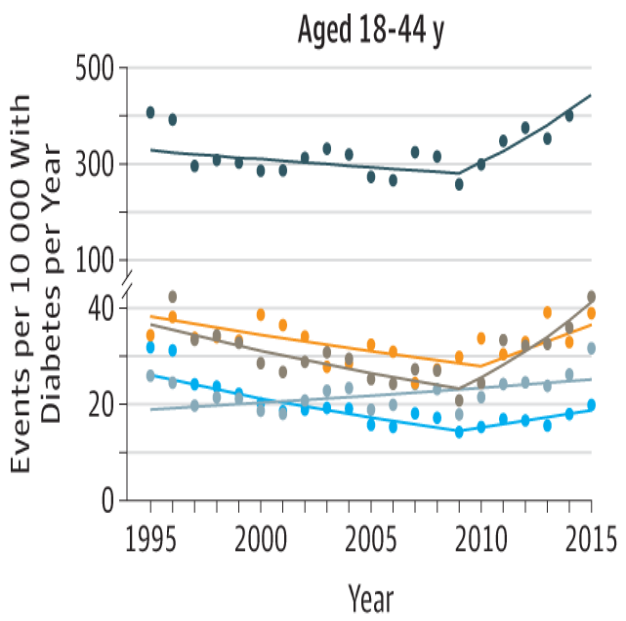
## Rajeev Gupta, MD, PhD

*Preventive Cardiology & Internal Medicine, Eternal Heart Care Centre & Research Institute, Mount Sinai New York Affiliate, Jaipur.*

*Academic Research Development Unit, Rajasthan University of Health Sciences, Jaipur.*

# Resurgence in Diabetes-Related Complications in USA

# *Cardiovascular Diseases and Diabetes*
# Emerging Themes in 2019

1. Renewed focus on healthy lifestyles

2. Tight diabetes control and new evidence (drugs) for prevention

3. Hypertension control

4. Lipid management: LDL-C, Triglycerides

5. Aspirin and CVD prevention

# Adherence to Healthy Lifestyle

# Strategies to decrease the impact of cardiovascular diseases in diabetes



Many risk factors of CVD in type 2 diabetes can be prevented by living a healthier lifestyle including:

a balanced diet

smoking cessation

more physical activity

It is vital that people with type 2 diabetes understand their **increased risk of CVD** and **what they can do** about it.

www.idf.org/takingdiabetes2heart

Source: Taking Diabetes to Heart Survey, International Diabetes Federation, 2018

www.idf.org/cvd

# Therapeutic Lifestyle Changes

| Parameter | Treatment Goal |
|---|---|
| **Weight loss (for overweight & obese patients)** | **Reduce by 5% to 10%** |
| **Physical activity** | • **150 min/week of moderate-intensity exercise(eg, brisk walking) plus flexibility and strength training** |
| **Diet** | • **Eat regular meals and snacks; avoid fasting to lose weight**<br>• **Consume plant-based diet (high in fiber, low calories/glycemic index, and high in phytochemicals/antioxidants)**<br>• **Understand Nutrition Facts**<br>• **Incorporate beliefs and culture into discussions**<br>• **Use mild cooking techniques instead of high-heat cooking**<br>• **Keep physician-patient discussions informal** |

6

# Intensive Glucose Control

# T2 Diabetes Mellitus: Effect of Intensive Glycemic Control (UKPDS)

3,867 patients with DM randomized to intensive therapy with a sulphonylurea or insulin (mean $HbA_{1C}$ 7.0%) or conventional therapy (mean $HbA_{1C}$ 7.9%)
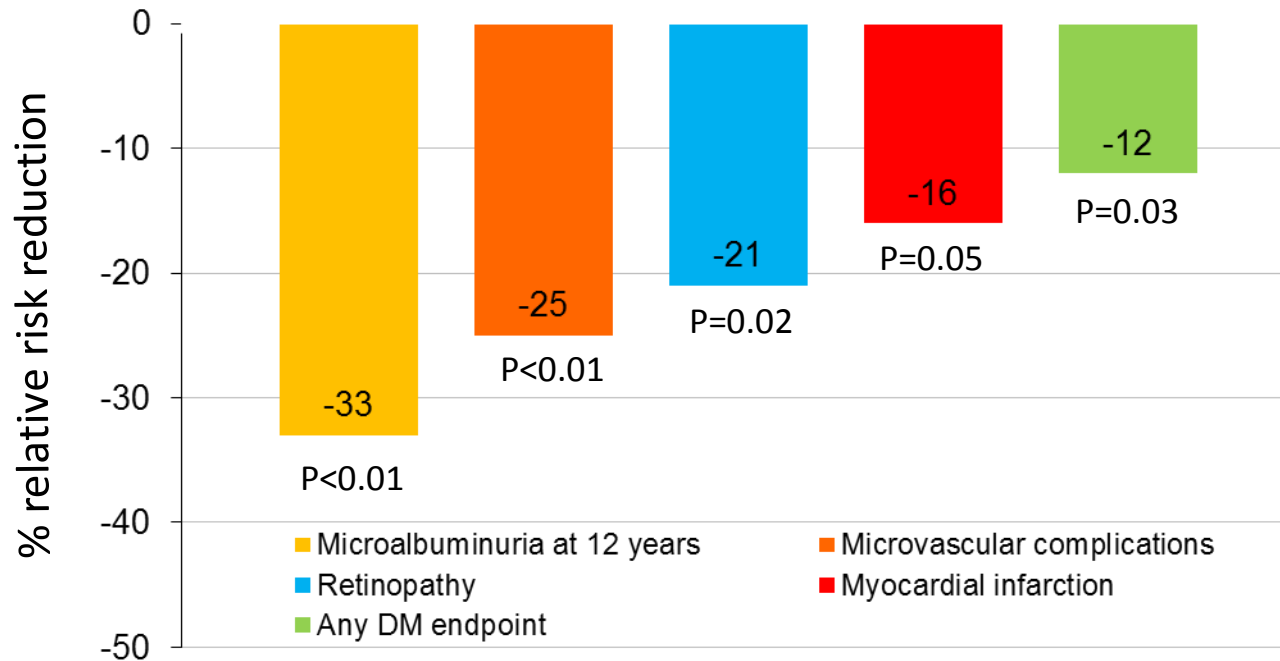


**Intensive glycemic control in DM reduces the risk of microvascular complications**

*UKPDS Group. Lancet 1998;352:837-853*

# T2DM: Effect of Good Glycemic Control

## United Kingdom Prospective Diabetes Study (UKPDS)
## 10-Year Follow-Up

Sulphonylurea vs. Conventional Therapy       Insulin vs. Conventional Therapy
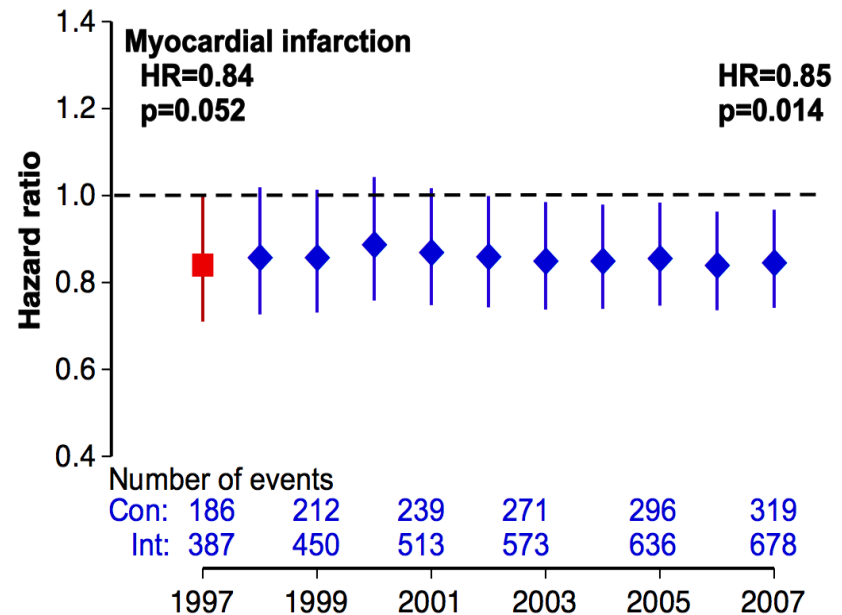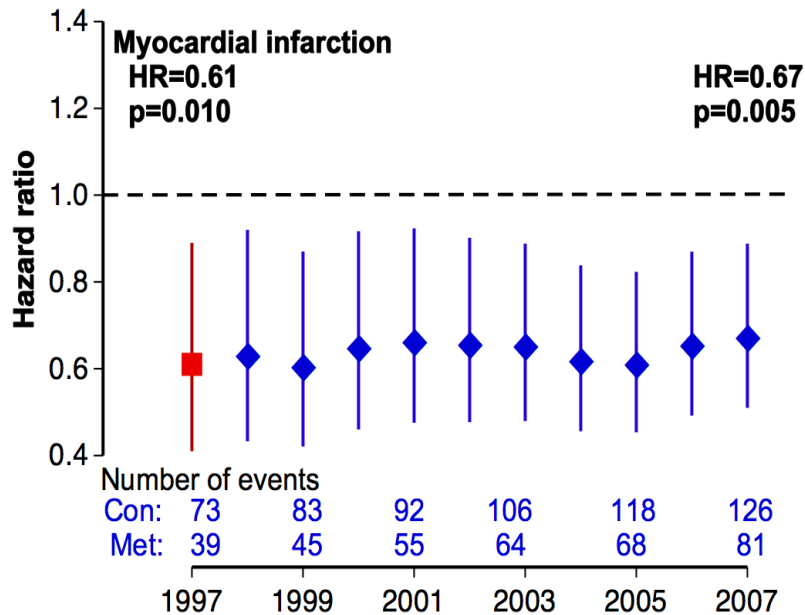


Intensive glycemic control in DM reduces the long-term risk of MI

*Holman RR et al. NEJM 2008;359:1577-1589*

# Anti-Diabetic Drugs for CV Protection and Prevention

# Cardiovascular Outcome Trials for Various Anti-Diabetes Drugs

| Quinquennium | Trial Name | Drugs Evaluated |
|---|---|---|
| Pre-1995 | DCCT<br>UKPDS | Insulin<br>Metformin |
| 1995-1999 | UKPDS | Hypoglycemic drugs |
| 2000-2004 | STOP-NIDDM<br>PRO-ACTIVE | Insulin<br>Pioglitazone |
| 2005-2009 | ACCORD, ADVANCE<br>VADT | Hypertension trials,<br>Multiple drugs |
| 2010-2014 | ORIGIN, DEVOTE<br>EXAMINE, SAVOR-TIMI<br>TECOS | Insulin<br>DPP4i |
| 2015+ | EMPAREG, CANVAS,<br>DECLARE-TIMI, CREDENCE<br><br>ELIXA, LEADER, EXSCEL,<br>LEADER | SGLT2i<br><br><br>GLP1RA |

# SGLT-2 Inhibitors and CAD Prevention Meta-Analysis

| | Patients | | Events | Events per 1000 patient-years | | Weight (%) | HR | HR (95% CI) |
|---|---|---|---|---|---|---|---|---|
| | Treatment (n/N) | Placebo (n/N) | | Treatment | Placebo | | | |
| **Patients with atherosclerotic cardiovascular disease** | | | | | | | | |
| EMPA-REG OUTCOME | 4687/7020 | 2333/7020 | 772 | 37·4 | 43·9 | 29·4 | | 0·86 (0·74–0·99) |
| CANVAS Program | 3756/6656 | 2900/6656 | 796 | 34·1 | 41·3 | 32·4 | Secondary 14% RRR | 0·82 (0·72–0·95) |
| DECLARE-TIMI 58 | 3474/6974 | 3500/6974 | 1020 | 36·8 | 41·0 | 38·2 | | 0·90 (0·79–1·02) |
| Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002) | | | | | | | | 0·86 (0·80–0·93) |
| **Patients with multiple risk factors** | | | | | | | | |
| CANVAS Program | 2039/3486 | 1447/3486 | 215 | 15·8 | 15·5 | 25·9 | | 0·98 (0·74–1·30) |
| DECLARE-TIMI 58 | 5108/10186 | 5078/10186 | 539 | 13·4 | 13·3 | 74·1 | Primary | 1·01 (0·86–1·20) |
| Fixed effects model for multiple risk factors (p=0·98) | | | | | | | | 1·00 (0·87–1·16) |

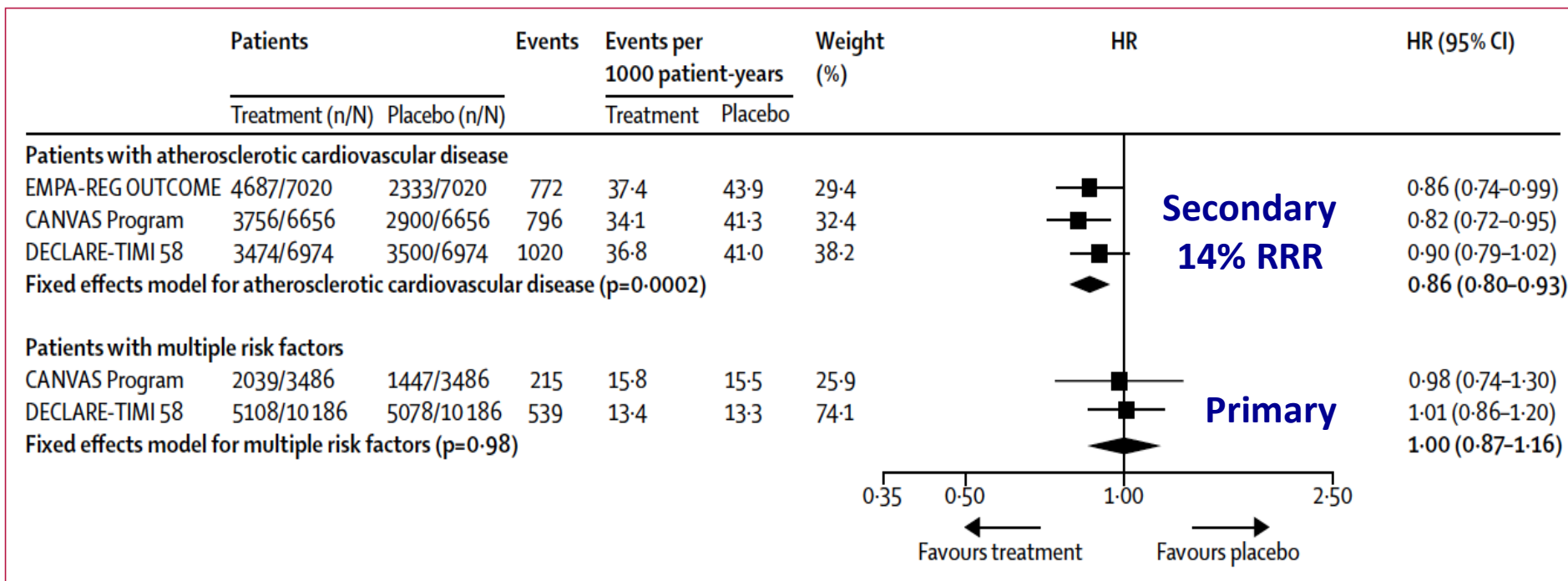HR scale: 0·35  0·50  1·00  2·50
Favours treatment ← → Favours placebo

Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

*Zelniker TA, et al. Lancet 2019;393:31-39*

# GLP1 Receptor Agonists and CAD Prevention Meta-Analysis

| Trial (n) | Drug | Outcome | OR | 95% CI |
|---|---|---|---|---|
| ELIXA (n=6068) | Lixisenatide | Primary<br>Secondary-MACE | 1.01<br>0.97 | 0.89-1.17<br>0.85-1.10 |
| LEADER (n=9340) | Liraglutide | Primary<br>Secondary-MACE | 0.87<br>0.88 | 0.78-0.98<br>0.81-0.96 |
| EXSCEL (n=14752) | Exenatide | Primary<br>Secondary-MACE | 0.91<br>0.88 | 0.83-1.00<br>0.76-1.02 |
| SUSTAIN-6 (n=3297) | Semaglutide | Primary<br>Secondary-MACE | 0.74<br>0.77 | 0.58-0.95<br>0.61-0.97 |

# Blood Pressure Control

# Diabetes Mellitus: Effect of Blood Pressure Control

## United Kingdom Prospective Diabetes Study (UKPDS)
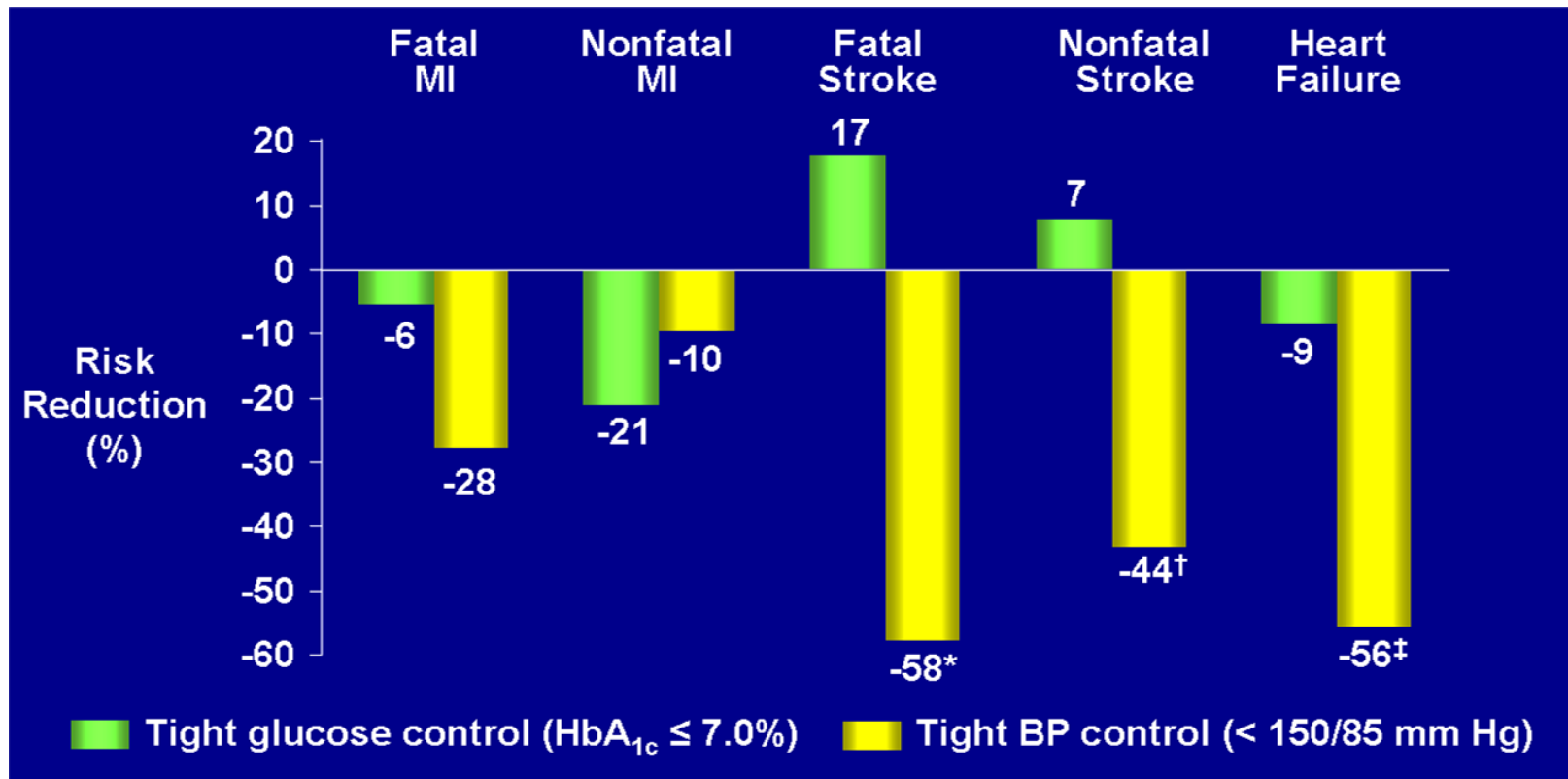


**BP control yields greater CV risk reduction than glycemic control**

**UKPDS 38.** *BMJ* 1998;317:703-713
**UKPDS 33.** *Lancet* 1998;352:837-853

# Diabetes Mellitus: Effect of an ACE Inhibitor
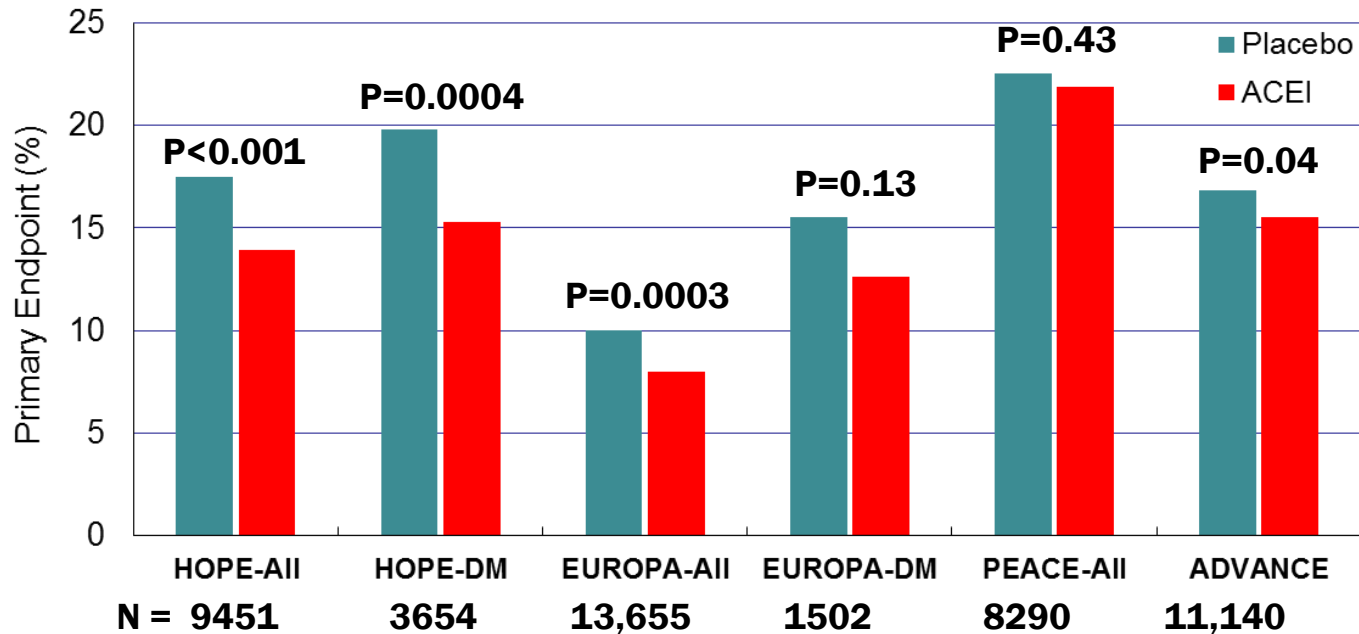


Use of an ACE inhibitor in most trials of DM is associated with a reduction in adverse CV events

Heart Outcomes Prevention Evaluation Study Investigators. *Lancet* 2000; 355: 253-259

Fox KM et al. *Lancet* 2003; 362: 782-788

Patel A et al. *Lancet* 2007; 370: 829-840

Daly CA et al. *Eur Heart J* 2005;14:1347-1349

The PEACE Trial Investigators. *NEJM* 2004;351:2058-2068

ADVANCE Collaborative Group. *NEJM* 2008;358:2560-2572

# Effect of Beta Blockade After an MI

Retrospective analysis of 45,308 patients with an acute MI to determine the impact of beta-blocker use on survival based on diabetic status
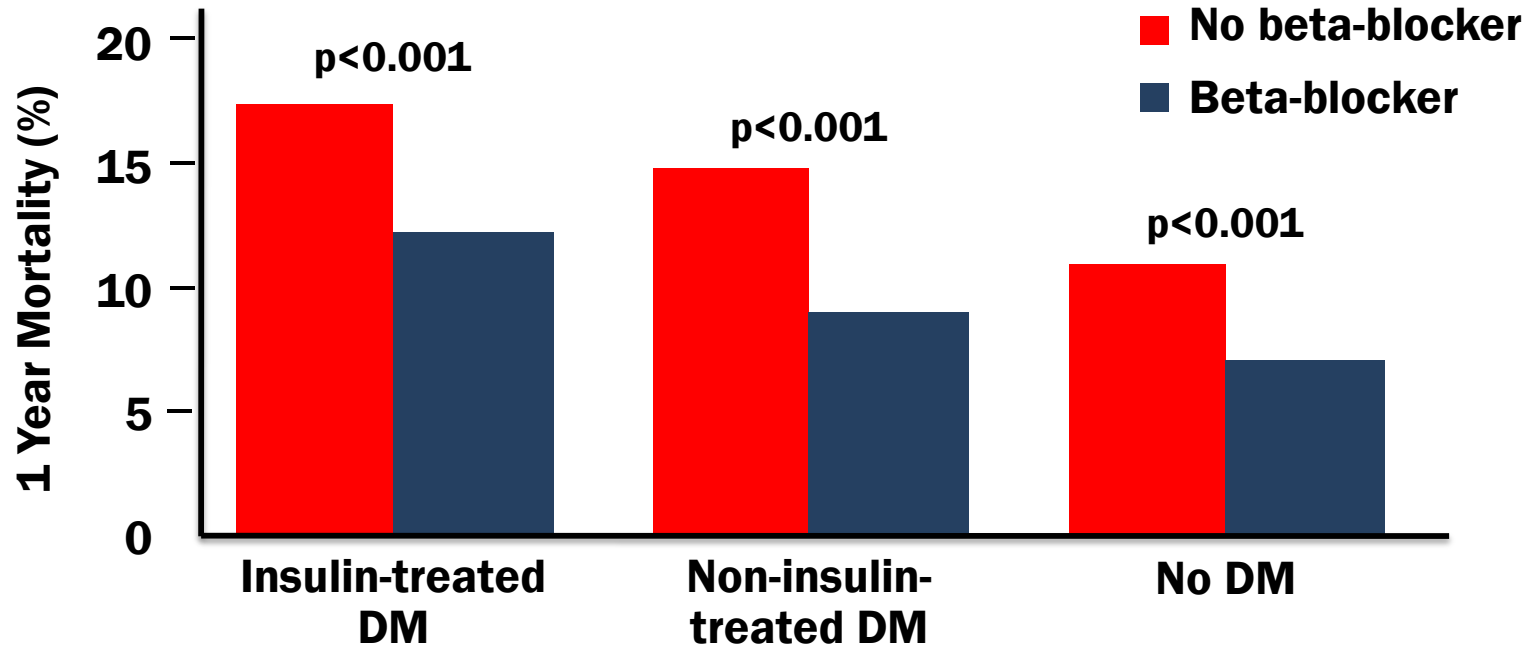


**Beta-blocker use in DM is associated with a mortality benefit similar to that seen in those without DM**

*Chen J et al. JACC 1999;34:1388-1394*

# Diabetes Mellitus: Effect of Tight BP Control

## Action to Control Cardiovascular Risk in Diabetes (ACCORD) Blood Pressure Trial

4,733 diabetic patients randomized to intensive BP control (target SBP <120 mm Hg) or standard BP control (target SBP <140 mm Hg) for 4.7 years
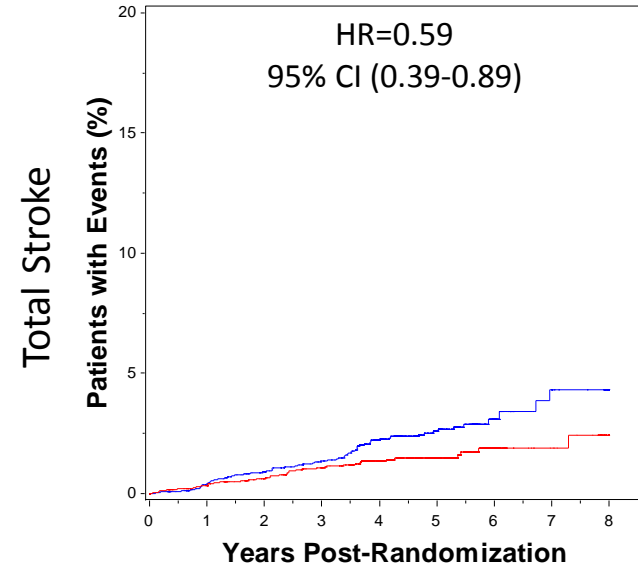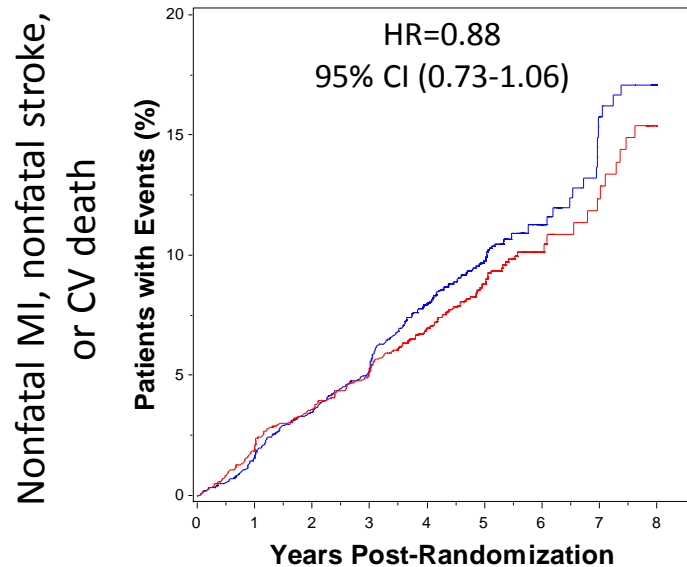


**Intensive BP control in DM does *not* reduce a composite of adverse CV events, but *does* reduce the rate of stroke**

ACCORD study group. *NEJM* 2010;362:1575-1585

# Hypertension Management in T2D in India
## Multisite Prescription Audit: India Heart Watch-2 (n=8699)

RAS blockers — DM+HTN: 48.2, DM+HTN+CVD: 58.1
Beta blockers — DM+HTN: 31.6, DM+HTN+CVD: 38.8
CC blockers — DM+HTN: 27.4, DM+HTN+CVD: 14.3
Diuretics — DM+HTN: 36.4, DM+HTN+CVD: 17.1

■ DM+HTN n=3625  ■ DM+HTN+CVD n=1131

*Gupta R, et al. JAPI. 2018;66(9):12-17*
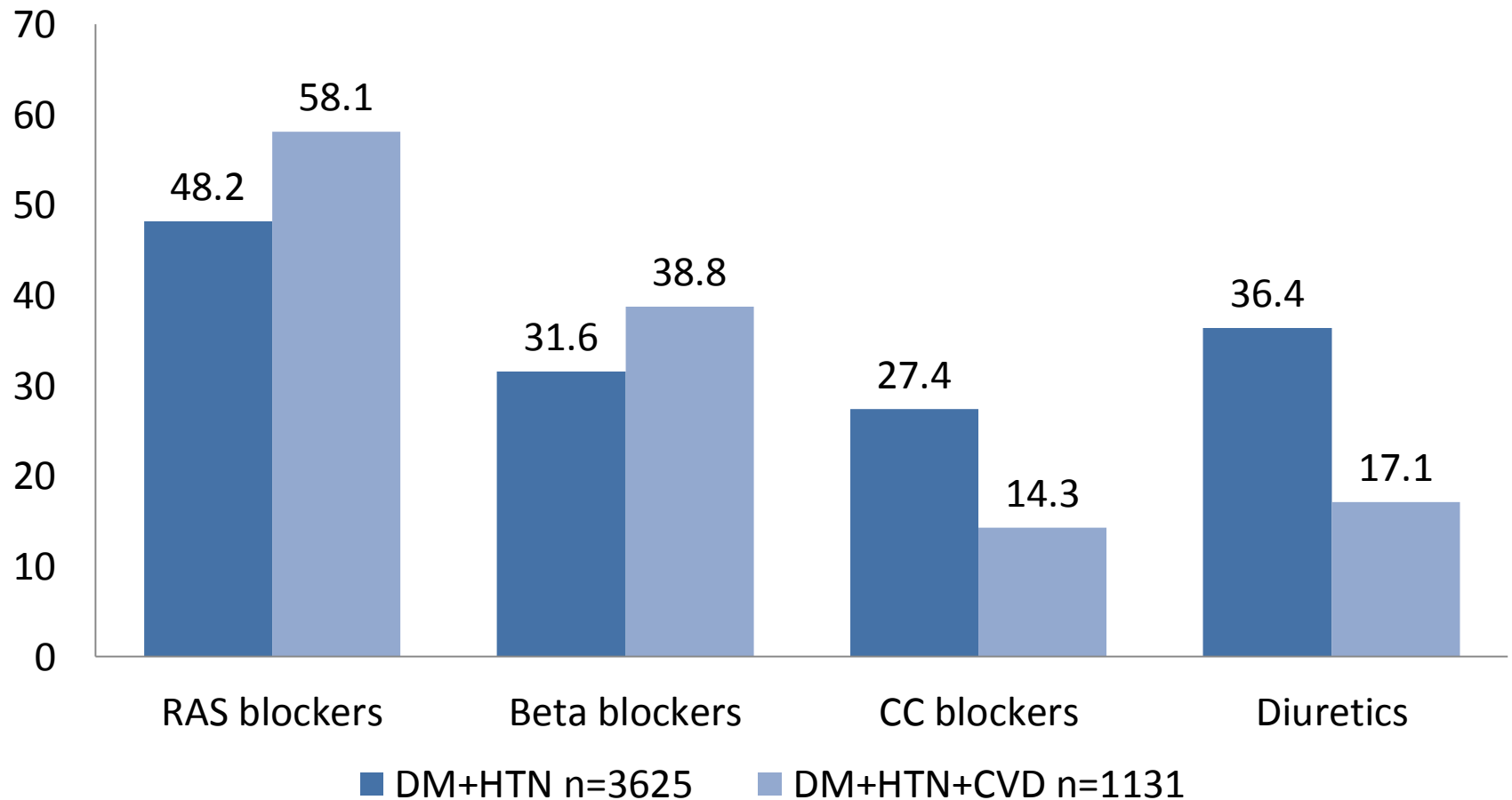
# Lipid Management

# Diabetes Mellitus: Effect of an HMG-CoA Reductase Inhibitor

## Collaborative Atorvastatin Diabetes Study (CARDS)

2,838 patients with type II DM and a baseline LDL-C ≤160 mg/dL randomized to atorvastatin (10 mg) or placebo for a median of 4 years



37% RRR (95% CI: 17-52), P=0.001

A statin reduces adverse CV events in diabetics

*Colhoun HM et al. Lancet 2004;364:685-696*

# Statins in Diabetes Meta-Analysis 2008

**Meta-analysis of 18,686 patients with DM randomized to treatment with a HMG-CoA Reductase Inhibitor**

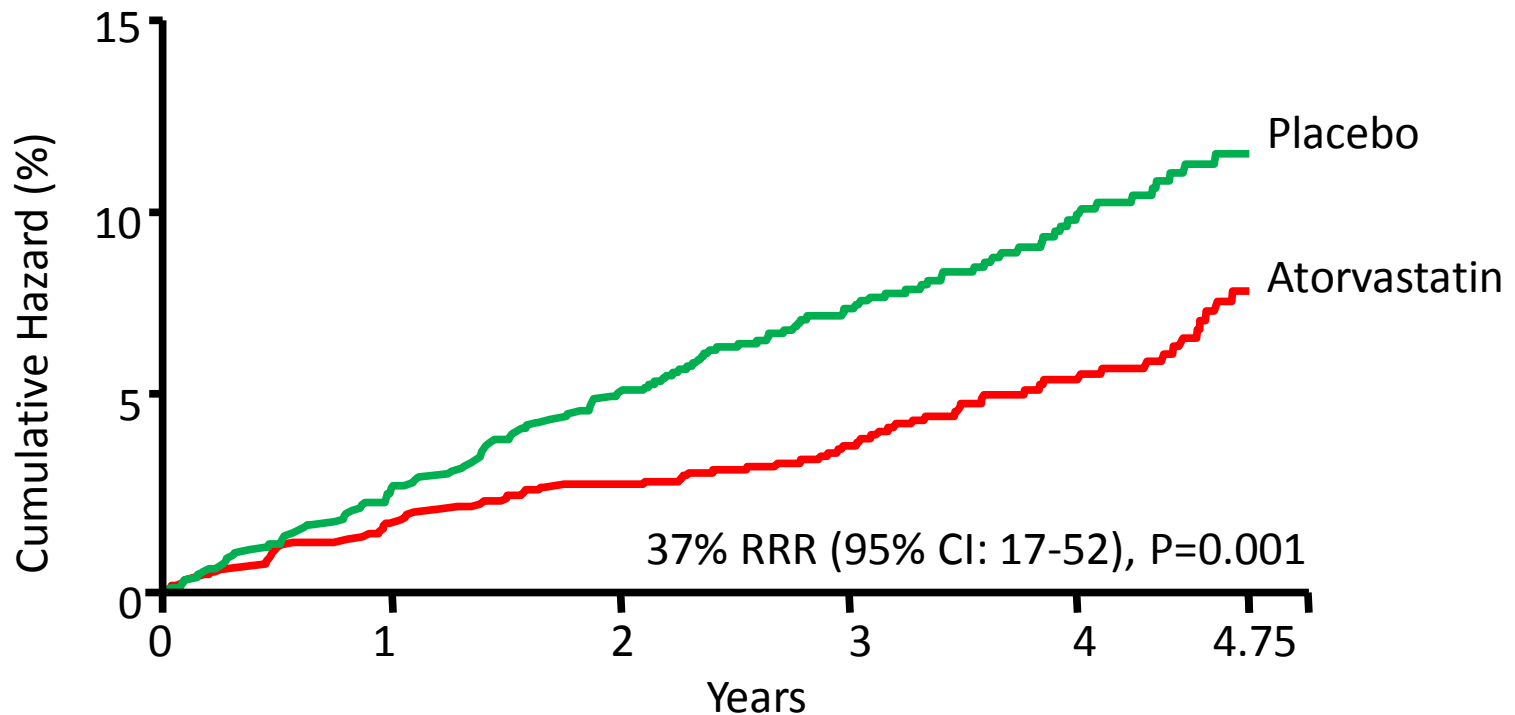| Major vascular event and prior diabetes | Events (%) Treatment | Events (%) Control | | RR (CI) |
|---|---|---|---|---|
| **Major coronary event** | | | | |
| Diabetes | 776 (8·3%) | 979 (10·5%) | | 0·78 (0·69–0·87) |
| No diabetes | 2561 (7·2%) | 3441 (9·6%) | | 0·77 (0·73–0·81) |
| **Any major coronary event** | **3337 (7·4%)** | **4420 (9·8%)** | | **0·77 (0·74–0·80)** |
| Test for heterogeneity within subgroup: $\chi^2_1=0·1$; p=0·8 | | | | |
| **Coronary revascularisation** | | | | |
| Diabetes | 491 (5·2%) | 627 (6·7%) | | 0·75 (0·64–0·88) |
| No diabetes | 2129 (6·0%) | 2807 (7·9%) | | 0·76 (0·72–0·81) |
| **Any coronary revascularisation** | **2620 (5·8%)** | **3434 (7·6%)** | | **0·76 (0·73–0·80)** |
| Test for heterogeneity within subgroup: $\chi^2_1=0·1$; p=0·8 | | | | |
| **Stroke** | | | | |
| Diabetes | 407 (4·4%) | 501 (5·4%) | | 0·79 (0·67–0·93) |
| No diabetes | 933 (2·7%) | 1116 (3·2%) | | 0·84 (0·76–0·93) |
| **Any stroke** | **1340 (3·0%)** | **1617 (3·7%)** | | **0·83 (0·77–0·88)** |
| Test for heterogeneity within subgroup: $\chi^2_1=0·8$; p=0·4 | | | | |
| **Major vascular event** | | | | |
| Diabetes | 1465 (15·6%) | 1782 (19·2%) | | 0·79 (0·72–0·86) |
| No diabetes | 4889 (13·7%) | 6212 (17·4%) | | 0·79 (0·76–0·82) |
| **Any major vascular event** | **6354 (14·1%)** | **7994 (17·8%)** | | **0·79 (0·77–0·81)** |
| Test for heterogeneity within subgroup: $\chi^2_1=0·0$; p=0·9 | | | | |

RR (99% CI)
RR (95% CI)

0·5  1·0  1·5
Treatment better    Control better

A statin reduces adverse CV events in diabetics

# Statins and CV Risk Reduction in Diabetes: 2016



| Presenting characteristics | Total number of MVEs | Annual event rate in control arm (% per year) | RR (CI) per 1 mmol/L reduction in LDL cholesterol | p value for heterogeneity or trend |
|---|---|---|---|---|
| **Pre-treatment LDL cholesterol (mmol/L)** | | | | p=0.22 |
| <2.5 | 5256 | 4.3 | 0.78 (0.69–0.89) | |
| ≥2.5 to <3.0 | 4182 | 4.0 | 0.77 (0.70–0.85) | |
| ≥3.0 to <3.5 | 4604 | 4.1 | 0.76 (0.70–0.82) | |
| ≥3.5 | 10563 | 3.9 | 0.80 (0.77–0.84) | |
| **Age (years)** | | | | p=0.14 |
| ≤65 | 13623 | 3.6 | 0.78 (0.75–0.82) | |
| >65 to ≤75 | 9211 | 4.6 | 0.79 (0.74–0.83) | |
| >75 | 2123 | 5.5 | 0.87 (0.76–0.99) | |
| **Sex** | | | | p=0.02 |
| Male | 19922 | 4.4 | 0.78 (0.75–0.81) | |
| Female | 5035 | 3.0 | 0.84 (0.78–0.91) | |
| **History of vascular disease** | | | | p=0.18 |
| **Diabetes** | | | | p=0.78 |
| Type 1 diabetes | 337 | 6.0 | 0.77 (0.58–1.01) | |
| Type 2 diabetes | 5621 | 5.1 | 0.80 (0.74–0.86) | |
| No diabetes | 18862 | 4.0 | 0.78 (0.76–0.82) | |
| **Treated hypertension** | | | | p=0.11 |
| Yes | 13939 | 4.5 | 0.80 (0.77–0.84) | |
| No | 10471 | 3.5 | 0.77 (0.73–0.81) | |
| **Smoking status** | | | | p=0.88 |
| Current smokers | 5225 | 4.7 | 0.79 (0.73–0.85) | |
| Non-smokers | 19728 | 3.9 | 0.79 (0.76–0.82) | |
| **5-year MVE risk** | | | | p=0.04 |
| <5% | 421 | 0.6 | 0.62 (0.47–0.81) | |
| ≥5 to <10% | 1453 | 1.6 | 0.69 (0.60–0.79) | |
| ≥10 to <20% | 7810 | 3.5 | 0.79 (0.74–0.85) | |
| ≥20 to <30% | 9028 | 5.8 | 0.81 (0.77–0.86) | |
| ≥30% | 6245 | 9.8 | 0.79 (0.74–0.84) | |
| **All patients** | 24957 | 4.0 | 0.79 (0.77–0.81) | |

■— 99% CI   ◇ 95% CI

0.5   0.75   1   1.25

LDL cholesterol lowering better — LDL cholesterol lowering worse

**23% RRR T1D**
**20% RRR T2D**

*Collins R, et al. Lancet 2016;388:2532-61*

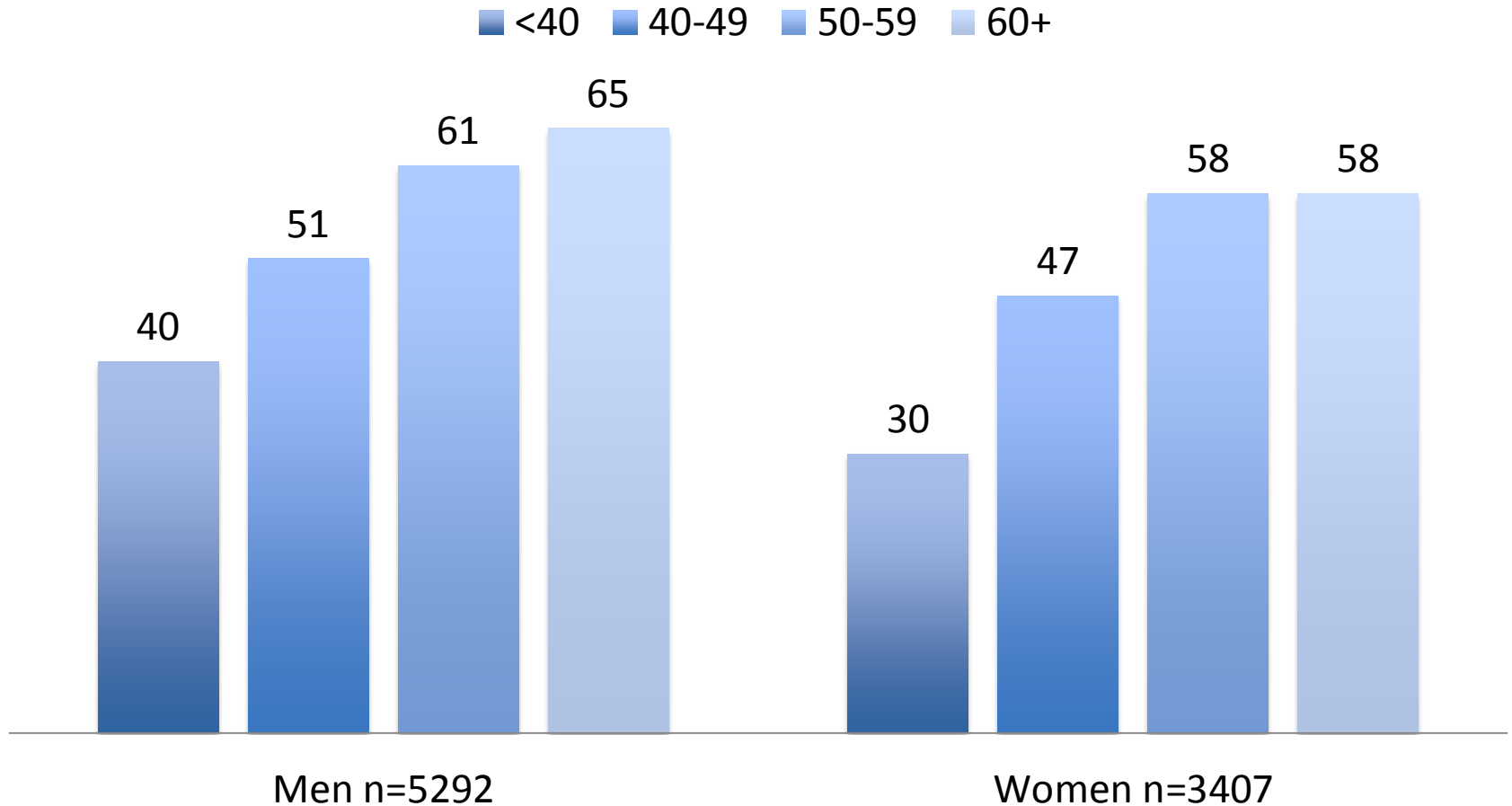# 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS /APhA/ASPC/PCNA Guidelines on the Management of Blood Cholesterol

In patients 40 to 75 years of age with diabetes mellitus and LDL cholesterol ≥70 mg/dl start moderate intensity statin therapy.

*2018 ACC/AHA Multisociety Guidelines. JACC 2018*
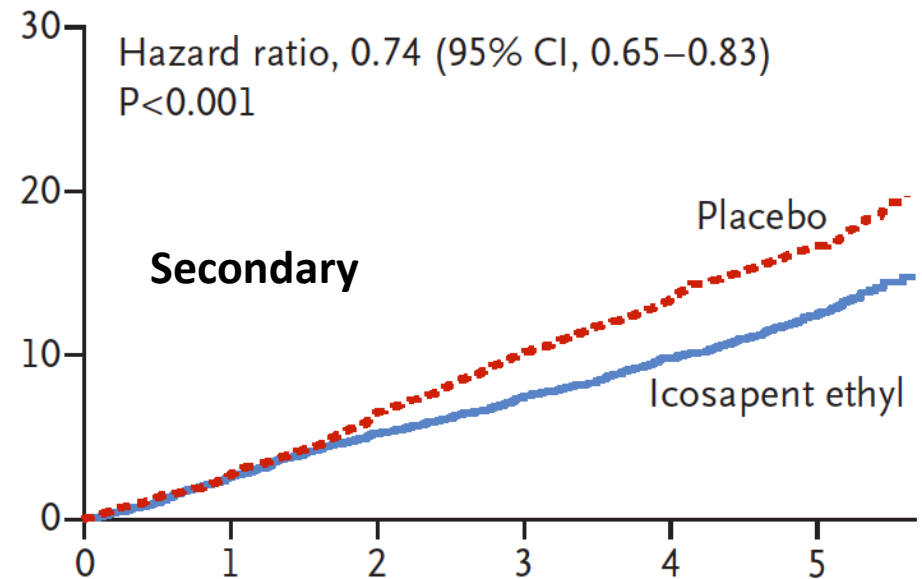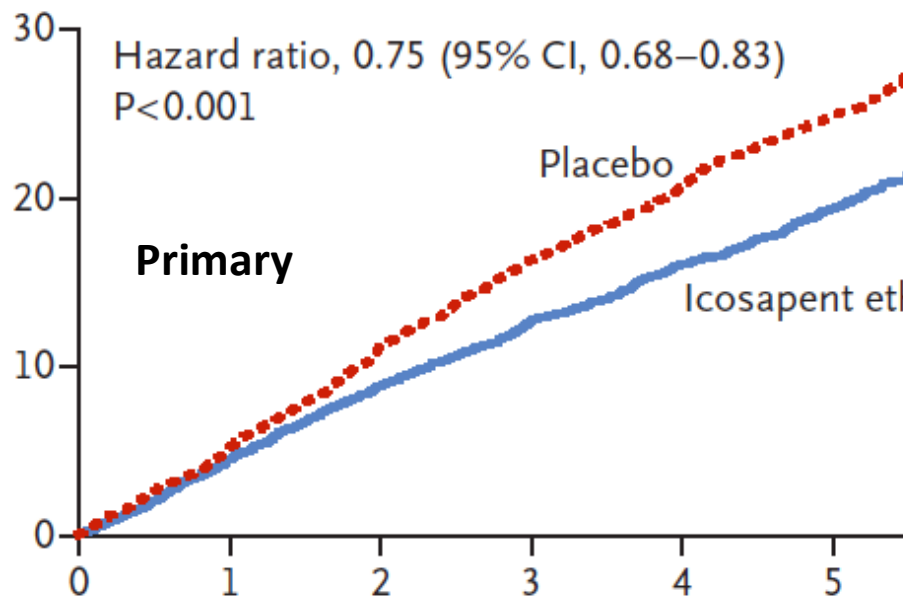*2019 ACC/AHA Prevention Guidelines. JACC 2019*

# Statin Use in Type 2 Diabetes in India
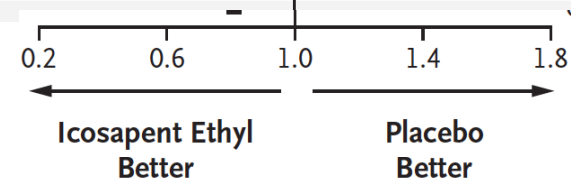## *India Heart Watch-2*

Legend: ■ <40  ■ 40-49  ■ 50-59  ■ 60+

Men n=5292: 40, 51, 61, 65

Women n=3407: 30, 47, 58, 58

*Gupta R, et al. BMJ Open Diabetes; 2016;4:e00275*

# Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia: REDUCE-IT



*Bhatt DL et al. N Engl J Med 2019:380:11-22*

# Aspirin for Primary Prevention: Dead!!

# Aspirin in Diabetes: 2010 Meta-Analysis

**Meta-analysis of 9 clinical trials evaluating the effect of aspirin on cardiovascular events among patients with diabetes mellitus**



| | Risk ratio |
|---|---|
| PHS | 0.59 (0.33,1.06) |
| ETDRS | 0.85 (0.73,1.00) |
| PPP | 0.49 (0.17,1.43) |
| WHS | 1.34 (0.85,2.12) |
| JPAD | 0.87 (0.40,1.87) |
| POPADAD | 1.09 (0.82,1.43) |
| TPT | 0.90 (0.28,2.89) |
| BMD | 1.00 (0.42,2.40) |
| HOT | 0.77 (0.44,1.36) |
| Overall (95% CI) | 0.91 (0.79,1.05) |
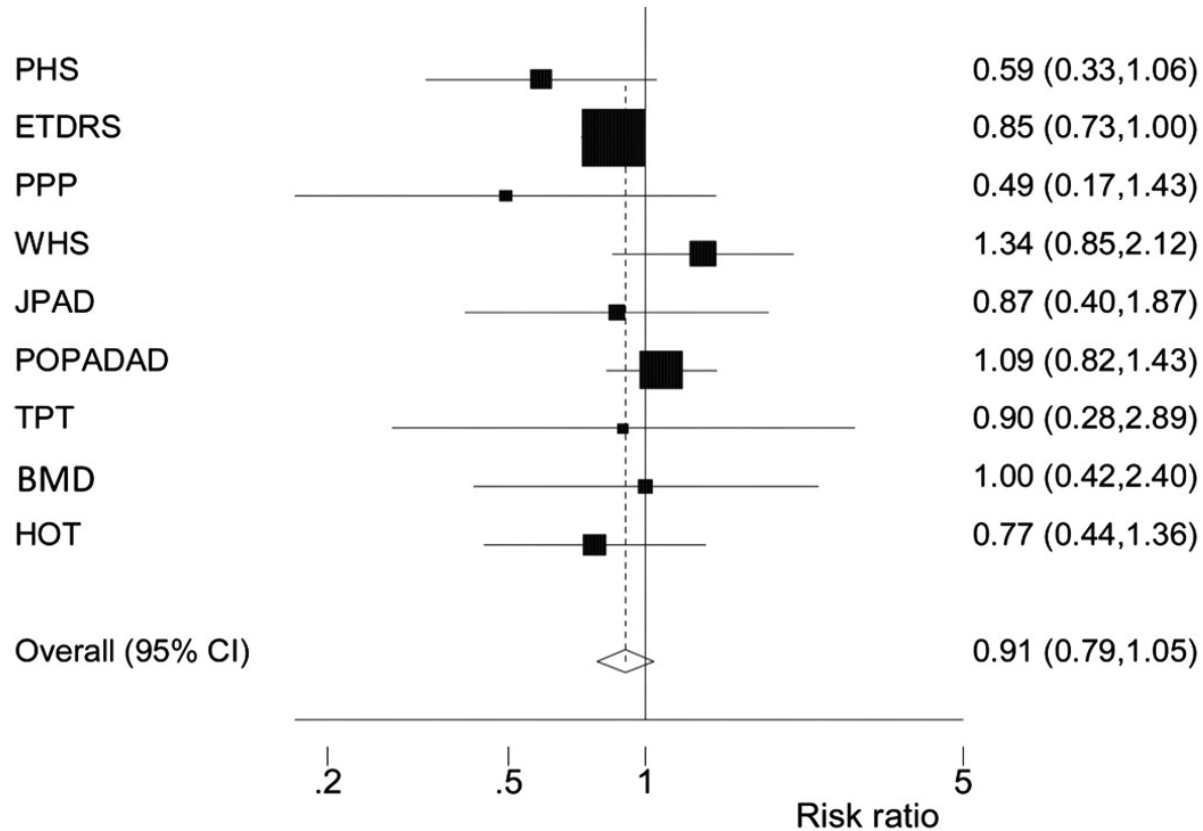
**Aspirin does not provide cardiovascular benefit in diabetics**

# Aspirin for Primary Prevention (in Diabetes)
## ARRIVE, ASPREE & ASCEND

Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial
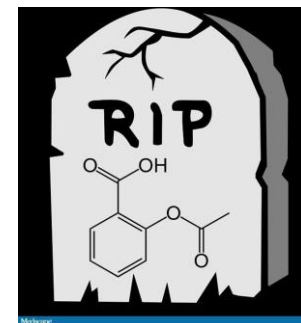
J Michael Gaziano, C...
Peter M Rothwell, Lu...

**Summary**
**Background** The...
to assess the eff...
cardiovascular ev...

ORIGINAL ARTICLE

Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly

J.J. McNeil, R. Wolfe, R.L. W...
C.M. Reid, J.E. Lockery, B...
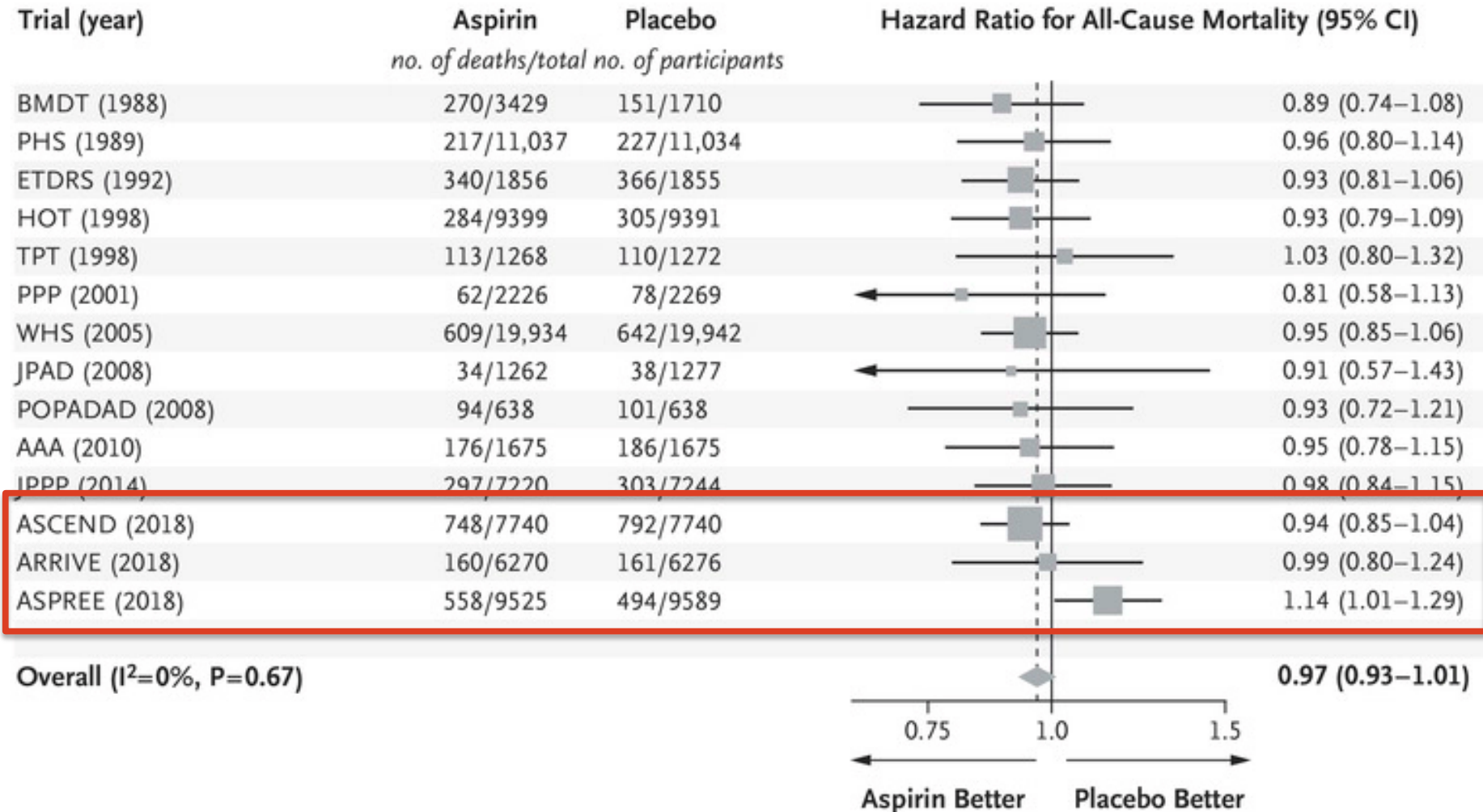K.L. Margolis, M.E. Ernst,...

ORIGINAL ARTICLE

Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus

The ASCEND Study Collaborative Group*

ABSTRACT

# Aspirin for Primary Prevention
# 14 Trials & Null Result

| Trial (year) | Aspirin | Placebo | Hazard Ratio for All-Cause Mortality (95% CI) | |
|---|---|---|---|---|
| | no. of deaths/total no. of participants | | | |
| BMDT (1988) | 270/3429 | 151/1710 | | 0.89 (0.74–1.08) |
| PHS (1989) | 217/11,037 | 227/11,034 | | 0.96 (0.80–1.14) |
| ETDRS (1992) | 340/1856 | 366/1855 | | 0.93 (0.81–1.06) |
| HOT (1998) | 284/9399 | 305/9391 | | 0.93 (0.79–1.09) |
| TPT (1998) | 113/1268 | 110/1272 | | 1.03 (0.80–1.32) |
| PPP (2001) | 62/2226 | 78/2269 | | 0.81 (0.58–1.13) |
| WHS (2005) | 609/19,934 | 642/19,942 | | 0.95 (0.85–1.06) |
| JPAD (2008) | 34/1262 | 38/1277 | | 0.91 (0.57–1.43) |
| POPADAD (2008) | 94/638 | 101/638 | | 0.93 (0.72–1.21) |
| AAA (2010) | 176/1675 | 186/1675 | | 0.95 (0.78–1.15) |
| JPPP (2014) | 297/7220 | 303/7244 | | 0.98 (0.84–1.15) |
| ASCEND (2018) | 748/7740 | 792/7740 | | 0.94 (0.85–1.04) |
| ARRIVE (2018) | 160/6270 | 161/6276 | | 0.99 (0.80–1.24) |
| ASPREE (2018) | 558/9525 | 494/9589 | | 1.14 (1.01–1.29) |
| Overall ($I^2$=0%, P=0.67) | | | | 0.97 (0.93–1.01) |

0.75   1.0   1.5

Aspirin Better     Placebo Better

# Conclusions: Emerging Themes for CVD Prevention in Diabetes: 2019

- **Lifestyle choices:**
  - **No tobacco policy (no smoking, smokeless tobacco)**
  - **Healthy foods: fruits, vegetables, nuts, legumes, dairy**
  - **Avoid unhealthy foods: high GI, trans fats, sat fats**
  - **Regular exercise: >150min/week moderate intensity**
- **Pharmaceutical interventions:**
  - **Tight diabetes control. Emerging role for SGLT2i**
  - **BP control ≅130/80 (2018 ESC/ESH guidelines): RASi**
  - **Statins in all diabetics (2018 US lipid guidelines)**
  - **Omega-3 fatty acids high dose (REDUCE-IT)**
  - **No aspirin**

# 2019: Artificial Intelligence in Medicine

- The promise of artificial intelligence in medicine is:
  - to provide composite panoramic view of individual's medical data,
  - to improve decision making
  - to avoid errors such as misdiagnosis and unnecessary procedures
  - to help in ordering and interpretation of appropriate tests, and
  - to recommend appropriate treatment.

Eric Topol. *Deep Medicine*. 2019