The PREDIMED study (Prevención con Dieta Mediterránea) examined whether Mediterranean-style eating supplemented with extra-virgin olive oil or nuts was superior to a low-fat diet for primary cardiovascular disease (CVD) prevention. The trial was stopped early after interim data showed a greater reduction in cardiovascular risk with a Mediterranean-style diet vs a low-fat (control) diet.

The primary endpoint, a composite of myocardial infarction (MI), stroke, or cardiovascular (CV) mortality, occurred among more patients in the low-fat diet group compared with the Mediterranean diet group. In practical terms, a Mediterranean-style diet supplemented with extra-virgin olive oil or nuts resulted in an absolute risk reduction of approximately 30% in high-risk subjects who were free from CVD at baseline.

With regard to secondary endpoints, a significant reduction in stroke was seen in the two Mediterranean diet groups compared with the control group; differences in the rates of MI, CV mortality, and all-cause mortality were not significant.

PREDIMED enrolled 7,447 subjects aged 55 to 80 years with no CVD at baseline; all had either type 2 diabetes or three or more CVD risk factors, including elevated LDL-C, low HDL-C, hypertension, overweight/obesity, or family history of premature coronary heart disease. Subjects were randomized in a 1:1:1 fashion to: Mediterranean diet + extra-virgin olive oil (24 tbsp/day; n=2,543), Mediterranean diet + nuts (30 g mixed nuts/day, including walnuts, almonds, and hazelnuts; n=2,454), or low-fat diet (control; n=2,450). No total calorie restriction was advised and no physical activity was promoted.

Niacin Adverse Events Halt the HPS2-THRIVE Trial

HPS2-THRIVE, a study examining extended-release (ER) niacin plus laropiprant (ERN/LRPT) vs placebo on time to first major vascular event in high-risk patients receiving statins for LDL-lowering, was stopped early due to significant adverse events observed among patients treated with ERN/LRPT. (See Box for more on niacin.)

A significantly higher number of subjects in the ERN/LRPT group stopped treatment vs subjects in the placebo group. Rates of adverse events leading to treatment discontinuation were more common in the ERN/LRPT group, with four times more skin-related reasons for discontinuation and twice as many gastrointestinal reasons for discontinuation, as well as nearly double the incidence of raised transaminases.

In the ERN/LRPT group, 25.4% of subjects stopped randomized treatment vs 16.6% in the placebo group (P<0.0001). (See Figure.) The proportion of patients who stopped taking study LDL-lowering treatment was also significantly higher in the ERN/LRPT group: 13.7% vs 11.7% placebo (P<0.0001).

Adverse events leading to treatment discontinuation in each group:
- Skin-related reasons were four times more common for ERN/LRPT: 5.4% vs 1.2% (P<0.0001)
- Gastrointestinal-related reasons were twice more common for ERN/LRPT: 3.9% vs 1.7% (P<0.0001)
- Musculoskeletal reasons were slightly more common for ERN/LRPT: 1.8% vs 1.0% (P<0.0001)
- Diabetes-related reasons were about twice as common for ERN/LRPT: 0.9% vs 0.4% (P<0.0001)

Allocation to ERN/LRPT nearly doubled the incidence of raised transaminases: alanine aminotransaminase (ALT) >3x upper limit of normal was 0.30%/year for ERN/LRPT and 0.14%/year for placebo (P<0.0001).

The risk for definite myopathy with ERN/LRPT was 4.4 (95% confidence interval [CI], 2.6-7.5; P<0.0001; 0.16%/year vs 0.04%/year). All patients who experienced myopathy had LDL-lowering and randomized treatments stopped. The excess risk was greater in Year 1 than in subsequent years.

Subjects in HPS2-THRIVE were at high risk for vascular disease and receiving effective statin-based LDL-lowering therapy. A total of 25,673 patients from China and Europe were randomized to ER niacin 2 g plus laropiprant 40 mg daily versus matching placebo. Background LDL-lowering therapy with simvastatin 40 mg or ezetimibe/simvastatin 10/40 mg was continued. All participants had occlusive arterial disease. The primary endpoint was time to a first major vascular event, a composite of nonfatal myocardial infarction (MI), cardiovascular (CV) mortality, stroke, or arterial revascularization.

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More on Niacin

Niacin (nicotinic acid) is commonly prescribed as an add-on to statin therapy for incremental lowering of LDL-C, apoB, Lp(a), and triglycerides (TG); and incremental increasing of HDL-C and apoA1. The use of niacin, particularly the extended-release (ER) formulation, is limited in clinical practice due to many adverse events, namely flushing. Laropiprant is an antagonist of DP1, the prostaglandin D2 receptor that mediates flushing; it has been shown to improve niacin tolerability.

The efficacy of niacin in reducing vascular risk among high-risk patients is unclear, particularly given the early discontinuation in 2011 of the Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) study after a mean of 3 years due to perceived lack of benefit in the treatment group allocated ER niacin 1.5-2.0 g/day plus statin.

In AIM-HIGH, there was no statistically significant difference in the percentage of subjects experiencing the primary endpoint, first event of the composite of coronary heart disease (CHD) death, nonfatal myocardial infarction (MI), ischemic stroke, hospitalization for acute coronary syndrome (ACS), or symptom-driven coronary or cerebral revascularization, between groups: 16.2% in the placebo + statin group and 16.4% in the niacin + statin group (hazard ratio [HR], 1.02; 95% confidence interval [CI], 0.87-1.21; P=0.80). Differences in the rate of the composite secondary endpoints (CHD mortality, nonfatal MI, high-risk ACS, or ischemic stroke; and CHD mortality, nonfatal MI, or ischemic stroke) were not statistically significant.
Cangrelor Reduces PCI Complications More than Clopidogrel in CHAMPION PHOENIX

Results from the Cangrelor versus Standard Therapy to Achieve Optimal Management of Platelet Inhibition (CHAMPION) PHOENIX study demonstrated a greater reduction in the composite primary efficacy endpoint of all-cause mortality, myocardial infarction (MI), ischemia-driven revascularization, or stent thrombosis 48 hours post-randomization among patients treated with cangrelor* vs clopidogrel, with a similar rate of adverse events between groups. (See Box for more on cangrelor.)

The rate of the primary efficacy endpoint was 4.7% in the cangrelor group and 5.9% in the clopidogrel group (odds ratio [OR], 0.78; 95% confidence interval [CI], 0.66-0.93; \( P = 0.005 \)). (See Figure.) The number needed to treat with cangrelor to prevent one primary endpoint event was 84 (95% CI, 49-285).

The rate of adverse events was similar between the cangrelor and clopidogrel groups: 20.2% vs 19.9% \( (P=0.13) \). In the cangrelor group, 0.5% of adverse events led to discontinuation of the study drug compared with 0.4% in the clopidogrel group \( (P=0.21) \). Transient dyspnea was significantly more frequent with cangrelor: 1.2% vs 0.3% with clopidogrel.

Rates of other key variables were as follows:

- **Primary efficacy endpoint at 30 days**: 6.0% in the cangrelor group and 7.0% in the clopidogrel group (OR, 0.85; 95% CI, 0.73-0.99; \( P = 0.03 \)).
- **Key secondary efficacy endpoint (incidence of definite stent thrombosis [ST]):** 0.8% in the cangrelor group and 1.4% in the clopidogrel group (OR, 0.62; 95% CI, 0.43-0.90; \( P = 0.01 \)).
- **Primary safety endpoint (Global Use of Strategies to Open Occluded Coronary Arteries [GUSTO] severe bleeding at 48 hours not related to coronary artery bypass grafting [CABG]):** 0.16% in the cangrelor group and 0.11% in the clopidogrel group (OR, 1.50; 95% CI, 0.53-4.22; \( P = 0.44 \)).
- **Intraprocedural stent thrombosis:** 0.6% in the cangrelor group and 1.0% in the clopidogrel group (OR, 0.65; 95% CI, 0.42-0.99; \( P = 0.04 \)).

CHAMPION PHOENIX assessed whether cangrelor reduces ischemic complications of percutaneous coronary intervention (PCI). A total of 10,942 patients were randomly assigned cangrelor or clopidogrel pre-PCI; all patients had stable angina, non–ST-segment elevation acute coronary syndrome (NSTE-ACS), or ST-segment elevation myocardial infarction (STEMI).

After randomization, patients were given a cangrelor infusion or matching placebo, and clopidogrel loading of 600 mg or 300 mg, or matching placebo. After the infusion, the cangrelor group received clopidogrel 600 mg, and the clopidogrel group received matching placebo. The study protocol also required: all patients to receive aspirin therapy (75-325 mg); clopidogrel 75 mg during first 48 hours, thereafter, clopidogrel or another P2Y\(_{12}\) inhibitor; periprocedural anticoagulant; and glycoprotein IIb/IIIa inhibitors as rescue therapy only.

* Cangrelor is an investigational agent that is not FDA approved for use in the United States.


**More on P2Y\(_{12}\) Receptor Inhibitors and GP IIb/IIIa Inhibitors**

- Antiplatelet therapies (P2Y\(_{12}\) receptor inhibitors and glycoprotein [GP] IIb/IIIa inhibitors) reduce ischemic event risk, especially stent thrombosis
- But, effect of these agents is often blunted as a result of complications during the acute phase of cardiovascular illness, as well as pharmacokinetic and pharmacodynamic variants
- Cangrelor: intravenous, fast-acting, potent, direct-acting adenosine diphosphate (ADP) P2Y\(_{12}\) inhibitor with quickly reversible effects

* Cangrelor is an investigational agent that is not FDA approved for use in the United States.
An ancillary observational analysis of Look AHEAD (Action for Health in Diabetes) showed a significantly greater likelihood of partial or complete type 2 diabetes remission among patients who received intensive lifestyle intervention compared with counterparts assigned to diabetes support and education.

In the first year, the prevalence of type 2 diabetes remission was 11.5% for the intensive lifestyle intervention group (95% confidence interval [CI], 10.1%-12.8%) compared with 2.0% in the diabetes support and education group (95% CI, 1.4%-2.6%). At Year 4, the rates were 7.3% (95% CI, 6.2%-8.4%) and 2.0 (95% CI, 1.5%-2.7%), respectively (P<0.001 for each year). (See Figure.)

Among participants who experienced partial or complete type 2 diabetes remission, one-third in the intensive lifestyle group returned to a clinical diabetes status each year: 33.1% (95% CI, 27.4%-39.3%) in Year 2; 33.8% (95% CI, 27.9%-40.2%) in Year 3; and 31.6% (95% CI, 25.3%-38.6%) in Year 4. Approximately one-half of participants in the diabetes support and education group returned to a clinical diabetes status each year: 52.4% (95% CI, 42.2%-62.3%) in Year 2; 45.9% (95% CI, 35.6%-56.6%) in Year 3; and 43.8% (95% CI, 32.9%-55.4%) in Year 4.

Participants in the intensive lifestyle group were more likely to experience continuous, sustained remission of type 2 diabetes: 9.2% (95% CI, 7.9%-10.4%) had at least a 2-year remission; 6.4% (95% CI, 5.7%-7.4%) had at least a 3-year remission; and 3.5% (95% CI, 2.7%-4.3%) had at least a 4-year remission. Rates for the diabetes support and education group: 1.7% (95% CI, 1.2%-2.3%; P<0.001) 2-year; 1.3% (95% CI, 0.8%-1.7%) 3-year; and 0.5% (95% CI, 0.2%-0.8%; P=0.02) for 4-year remission. (See Figure.) Any remission of type 2 diabetes during the first year of the study was significantly associated with shorter diabetes duration, low body mass index, low baseline A1C, no insulin use, and greater 1-year weight loss.

This analysis, which included 4,530 Look AHEAD participants (n=2,241 in lifestyle group n=2,262 in diabetes support and education group), examined the association of a long-term intensive lifestyle intervention with remission (partial or complete) of type 2 diabetes. Median time since diabetes diagnosis was 5 years; mean body mass index was 35.8 kg/m². The Look AHEAD trial assessed long-term effects (up to 11.5 years) of intensive lifestyle intervention over 4 years on cardiovascular (CV) morbidity and mortality among overweight, obese individuals with type 2 diabetes who were randomized to intensive lifestyle intervention or diabetes support and education.1


In this first-ever study comparing treatment with once-weekly exenatide and once- or twice-daily insulin detemir in patients with type 2 diabetes inadequately controlled with oral antidiabetes drugs (OADs), patients receiving once-weekly exenatide were 6.6 times more likely to achieve the primary outcome of A1C ≤7.0% and ≥1.0 kg weight loss* versus subjects receiving insulin.

At 26 weeks, a total of 44.1% of subjects receiving once-weekly exenatide (95% confidence interval [CI], 34.7%-53.9%) and 11.4% of those receiving insulin detemir (95% CI, 6.0%-19.1%) met the primary endpoint of A1C ≤7.0% and ≥1.0 kg weight loss. Higher baseline A1C reduced the chance of achieving the primary endpoint (P<0.05). (See Figure.)

The mean change in A1C was -1.3% (95% CI, -1.45% to -1.14%) among participants receiving once-weekly exenatide and -0.88% (95% CI, -0.93% to -0.82%) for the insulin detemir group. The treatment difference between groups was -0.42% (95% CI, -0.63% to -0.21%; P<0.0001).

Proportion of patients who achieved A1C targets:
- A1C ≤7.4%: 67% exenatide vs 54% detemir (P=0.0497)
- A1C ≤7.0%: 51% exenatide vs 34% detemir (P=0.007)
- A1C ≤6.5%: 28% exenatide vs 8% detemir (P=0.0002)

Mean body weight change* was -2.68 kg (-3.4 to -2.0) among patients receiving once-weekly exenatide and +0.8 kg (0.1 to 1.5) for insulin detemir. The treatment difference between groups was -3.5 kg (95% CI, -4.4 to -2.6; P<0.0001).

Participants enrolled in this 26-week, phase 3, randomized, open-label, parallel-arm, active-comparator study were aged ≥18 years and had type 2 diabetes, A1C ≥7.1% to ≤10.0% despite therapy with metformin alone or metformin plus sulfonylurea, stable weight for 3 months, and body mass index 25-45 kg/m². Randomization was to once-weekly exenatide (2 mg; n=111) or once- or twice-daily insulin detemir (n=105). Any current OADs were continued. Subjects were stratified by baseline A1C (≥7.0% to <8.5% or ≥8.5% to ≤10.0%). The primary outcome was the proportion of patients with A1C ≤7.0% and ≥1.0 kg weight loss at 26 weeks. Several secondary outcomes, including glycemic control, cardiovascular risk factors, safety, and tolerability, were also assessed.

*Study drugs not indicated for weight loss


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A retrospective cohort analysis assessing the impact of early hypertension control on the occurrence of cardiovascular (CV) events in patients with diabetes and recent-onset hypertension showed a decrease in blood pressure (BP) after hypertension onset.

Mean BP decreased to 131.4/78.0 mm Hg one year after onset of hypertension. A total of 32.9% of subjects had mean BP <130/80 mm Hg; 80.2% of subjects had mean BP <140/90 mm Hg. Age adjusted rates of major CV events over 3.2 years among subjects (P=0.004):
- Mean BP <130/80 mm Hg: 5.10 events/1,000 person-years
- Mean BP ≥140/90 mm Hg: 6.94 events/1,000 person-years

A total of 15,665 adults with diabetes and no coronary or cerebrovascular disease were enrolled in the study; mean age was 51.5 years and mean baseline BP was 136.8/80.8 mm Hg.

A n analysis of data from the ACCORD study (Action to Control Cardiovascular Risk in Diabetes) examining the effect of interventions on retinal pathology at baseline and after 4 years’ follow-up showed that individuals with progressively greater severity of retinopathy at baseline had higher baseline A1C and systolic blood pressure \( (P \text{ for trend} <0.0001) \) and were more likely to experience the ACCORD primary endpoint of myocardial infarction [MI] or stroke \( (P<0.001) \).

Individuals with worsening of retinopathy over 4 years had progressively higher A1C levels, systolic blood pressure, and LDL-C at baseline \( (P<0.01) \) and were more likely to experience the ACCORD primary endpoint \( (P<0.001) \) and MI \( (P=0.01) \). The hazard ratio (HR) for the primary endpoint increased by 38% \( \text{HR, 1.38; 1.10-1.74} \) for each change in retinopathy severity. The hazard ratio for MI increased by 40% \( \text{HR, 1.40; 1.08-1.80} \) for every change in retinopathy severity.

The present study assessed data to confirm the relationship between severity of baseline retinopathy and cardiovascular (CV) outcomes, and to determine whether deterioration of retinopathy with time is linked to CV outcomes among 2,856 participants (mean age 61 years) from the ACCORD Eye study who had baseline retinal photographs. ACCORD Eye assessed the effects of the interventions used in ACCORD on the development or progression of retinopathy. ACCORD was a randomized, multicenter, double 2X2 factorial trial in patients with type 2 diabetes designed to test the effects on major cardiovascular events of intensive glycemia control, of fibrate treatment to increase HDL-C and lower triglycerides, and of intensive blood pressure control, each compared to an appropriate control.\(^1\)


The Diabetes Heart Study sought to examine whether coronary artery calcium (CAC) provides additional prognostic information regarding cardiovascular disease (CVD) mortality—beyond traditional Framingham Risk Score (FRS) factors—among patients with type 2 diabetes. Study findings showed a higher incidence of CVD mortality in higher CAC categories.

The odds ratios (95% confidence interval [CI]) for CVD mortality using CAC scores 0-9 as the reference group were: (See Figure.) \( \bullet \) CAC 10-99: 2.93 (0.74-19.55; \( P=0.13 \)) \( \bullet \) CAC 100-299: 3.17 (0.70-22.22; \( P=0.13 \)) \( \bullet \) CAC 300-999: 4.41 (1.15-29.0; \( P=0.03 \)) \( \bullet \) CAC \( \geq \)1,000: 11.23 (3.24-71.0; \( P=0.0001 \))

Over 7.4 years of follow-up in the Diabetes Heart Study, 92 deaths were attributed to CVD:

- Myocardial infarction (MI): 40
- Coronary artery disease (CAD): 24
- Cardiac arrest: 12
- Congestive heart failure (CHF): 12
- Stroke: 4

The Diabetes Heart Study examined the risk of CVD mortality among patients with type 2 diabetes across a range of CAC scores, and also evaluated the extent to which adding CAC to a prediction model based on FRS factors accurately stratifies future CVD mortality risk among patients with type 2 diabetes. The study enrolled 1,123 patients with type 2 diabetes: mean age, 61 years; 86% had CAC score \( \geq \)10; average follow-up, 7.4 years. The primary endpoint was cardiovascular mortality after CAC screening.