Assessment of Risk Reduction of Recurrent Cardiovascular Events in Patients With ASCVD and Diabetes

Nathan D. Wong[1], PhD, MPH; Hridhay Karthikeyan[1], MS; Wenjun Fan[1], MD, PhD; Nafeesa Dhalwani[2], PhD; Lisa Head[2], PharmD; Ran Jin[2], PhD

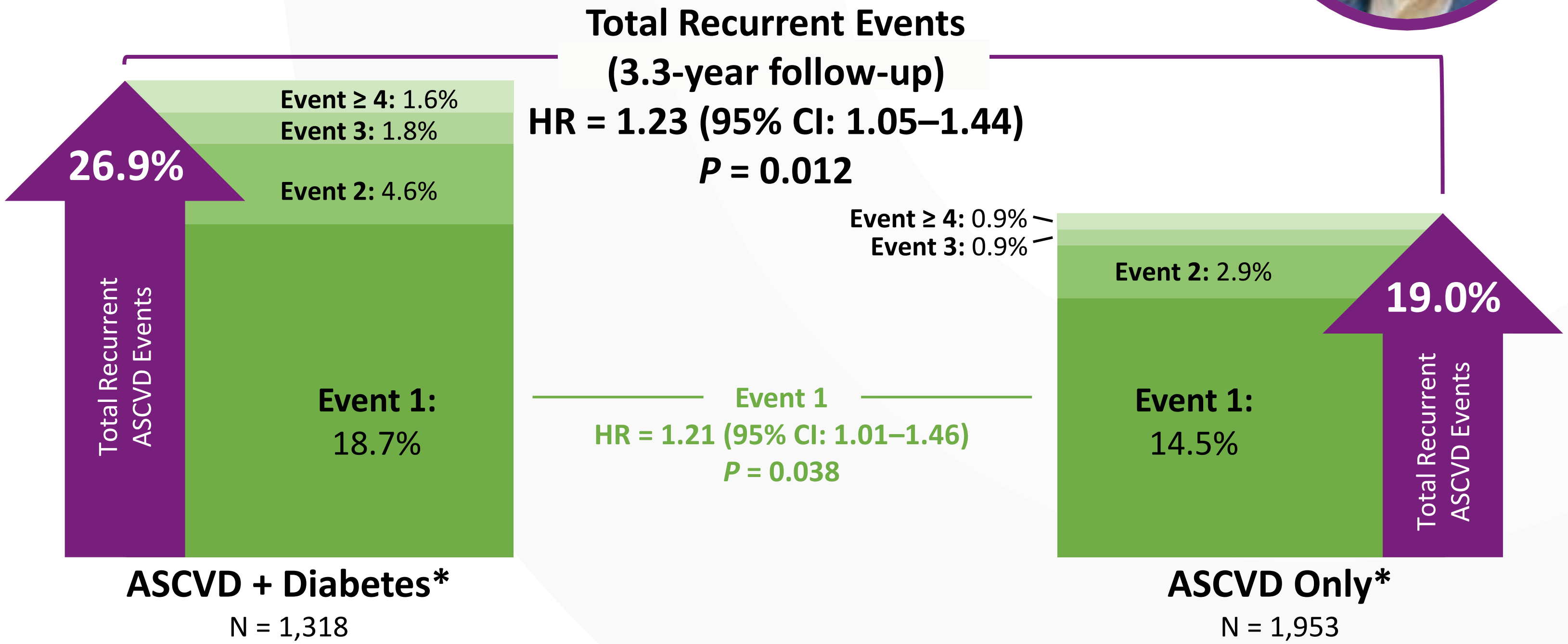
[1]Heart Disease Prevention Program, Mary and Steve Wen Cardiovascular Division, Center for Global Cardiometabolic Health and Nutrition, University of California, Irvine, CA, USA

[2]Amgen Inc., Thousand Oaks, CA, USA

This study was funded by Amgen. Medical writing assistance provided by Stacie Meaux, PhD, Red Nucleus.

Study Background

- Patients with ASCVD and diabetes are at increased risk for recurrent ASCVD events, especially when modifiable risk factors are poorly controlled[1]



However, predicted risk reduction and its population impact by controlling risk factors such as LDL-C, HbA1c, and BMI individually or in combination among patients with ASCVD and DM have not yet been quantified.

Figure adapted from Zhao Y, et al. *J Diab Complications*. 2021;35:107767.

*Based on 3,271 patients with ASCVD on statin therapy in the AIM-HIGH clinical trial cohort. HRs were adjusted for age, sex, White race, SBP, DBP, BMI, LDL-C, HDL-C, triglycerides, Lp(a), smoking status, alcohol use, serum creatinine, homocysteine, history of CVD, hypertension medication and randomized treatment.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CI, confidence interval; CVD, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; HR, hazard ratio; LDL-C, low-density lipoprotein cholesterol; Lp(a), lipoprotein (a); SBP, systolic blood pressure.

1. American Diabetes Association Professional Practice Committee. *Diabetes Care*. 2025;48:S207-S238.

Study Design and Objectives

Primary objective: To predict the 3-year risk reduction of the composite of nonfatal/fatal MI and ischemic stroke and of the number of preventable events by achieving guideline-based thresholds[1-3] for HbA1c and LDL-C, individually and in combination

Secondary objective: To predict the 3-year risk reduction of the composite of nonfatal/fatal MI and ischemic stroke and of the number of preventable events in the subset of patients with a BMI of ≥ 27 kg/m^2, from individual control and co-management of LDL-C, HbA1c, and BMI

NHANES (2011–2020)

- Age ≥ 18 years
- ASCVD* & LDL-C ≥ 70 mg/dL
- DM† & HbA1c ≥ 7%
- BMI ≥ 27 kg/m^2 *(subset for secondary objective)*

Predicted 3-year risk of MI/stroke using TIMI Risk Score-MACE DM[4] and risk reduction with risk factor control

Primary objective

Secondary objective

Simulated Scenarios for Risk Reduction

- LDL-C = 70 mg/dL (or 55 mg/dL)
- HbA1c = 7.0%
- BMI = 25 kg/m^2
- LDL-C = 70 mg/dL (or 55 mg/dL) + HbA1c = 7.0%
- LDL-C = 70 mg/dL (or 55 mg/dL) + BMI = 25 kg/m^2
- HbA1c = 7.0% + BMI = 25 kg/m^2
- LDL-C = 70 mg/dL (or 55 mg/dL) + HbA1c = 7.0% + BMI = 25 kg/m^2

*Prior MI, coronary heart disease, or stroke. †Self-report of physician diagnosis of DM, glycated HbA1c ≥ 6.5%, glucose of ≥ 126 mg/dL (fasting) or ≥ 200 mg/dL (non-fasting), or use of insulin or hypoglycemic medication.

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; TIMI, thrombolysis in myocardial infarction.

1. Grundy SM, et al. *Circulation*. 2019:139;e1082-e1143. 2. Lloyd-Jones DM, et al. *J Am Coll Cardiol.* 2022:80;1366-1418. 3. American Diabetes Association Profession Practice. *Diabetes Care*. 2025:48;S207-S238. 4. Berg DD, et al. *J Am Coll Cardiol*. 2023;81:2391-2402.

Estimation of Recurrent ASCVD Risk Using TIMI Risk Score

- **Relative Risk Reduction (RRR)**
  - Baseline risk: computed from baseline characteristics
  - The predicted risk: calculated after setting HbA1c (7%), LDL-C (70 mg/dL or 55 mg/dL), and BMI (25 kg/m^2, for secondary objective only) to guideline-based levels
  - RRR = % (baseline risk – predicted risk) / (baseline risk)
- **Estimation of preventable ASCVD events**
  - Computed RRR were multiplied by the sample population, then extrapolated to the US population by NHANES sample weights

Parameter	Beta Coefficient
Age (years)	
65–74	0.263
≥ 75	0.539
Sex	
Male	0.285
BMI	0.011
LDL-C	0.005
SBP (mmHg)	
140–159	0.141
≥ 160	0.406
Tobacco use	0.318
Insulin use	0.262
HbA1c	0.041

Parameter	Beta Coefficient
eGFR < 60	0.202
UACR	
30 to < 300	0.233
≥ 300	0.451
Comorbidity	
CAD	0.474
Prior MI	0.287
Prior PCI	0.397
Prior CABG	0.293
Ischemic stroke	0.696
PAD	0.270

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary heart disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL-C low-density lipoprotein cholesterol; MI, myocardial infarction; NHANES, National Health and Nutrition Examination Survey; RRR, relative risk reduction; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIMI, thrombolysis in myocardial infarction; UACR, urine albumin-to-creatinine ratio.

Eligible Sample Selection From the NHANES (2011–2020)

n = 22,824 (N = 283,601,158)

→ n = 6511 (N = 42,719,929) aged < 18 years

n = 16,313 (N = 240,881,229)

→
- n = 14,821 (N = 222,726,454) no ASCVD
- n = 835 (N = 10,825,790) no DM

n = 657 (N = 7,328,985)

→
- n = 344 (N = 3,484,792) LDL-C < 70 mg/dL
- n = 182 (N = 2,109,396) HbA1c < 7%

Primary Analysis Sample

n = 131 (N = 1,734,797)
Aged 18+, with ASCVD, DM, HbA1c ≥ 7%, LDL-C ≥ 70 mg/dL

→ n = 20 (N = 204,925) BMI < 27 kg/m^2

Secondary Analysis Sample

n = 111 (N = 1,529,872)
Aged 18+, with ASCVD, DM, HbA1c ≥ 7%, LDL-C ≥ 70 mg/dL, BMI ≥ 27 kg/m^2

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; N, representative weighted population; n, sample size; NHANES, National Health and Nutrition Examination Survey.

Characteristics of Eligible NHANES Participants

Characteristic, mean ± SEM or n (%)	Primary Sample n = 131 N = 1.73 M	Secondary Sample n = 111 N = 1.53 M
Age (years)	63.3 ± 0.9	62.7 ± 0.8
Sex (male)		
Male	78 (69.6)	66 (68.2)
BMI (kg/m²)	34.8 ± 0.9	36.1 ± 0.5
Blood pressure (mmHg)		
Systolic	132.4 ± 2.1	131.8 ± 2.2
Diastolic	69.4 ± 1.1	69.6 ± 1.0
LDL-C levels (mg/dL)	110.9 ± 3.0	111.3 ± 2.8
eGFR (mL/min/1.73 m²)	75.3 ± 1.8	76.3 ± 1.9
HbA1c (%)	8.9 ± 0.2	9.0 ± 0.2

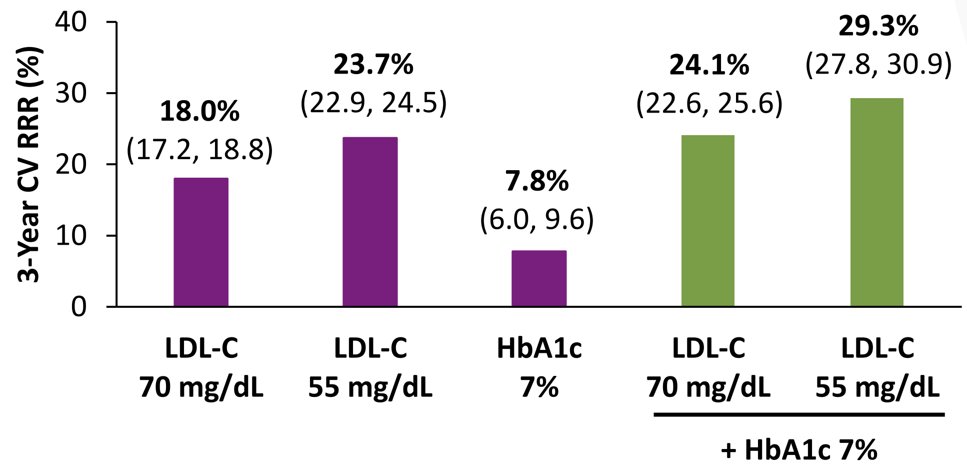
Characteristic, mean ± SEM or n (%)	Primary Sample n = 131 N = 1.73 M	Secondary Sample n = 111 N = 1.53 M
ASCVD history		
CAD	56 (45.2)	49 (46.0, 0.70)
MI	64 (44.3)	52 (43.8, 0.67)
Ischemic stroke	47 (40.9)	41 (41.1, 0.63)
PAD*	10 (7.6)	8 (7.2, 0.11)
Insulin usage	69 (48.4)	56 (47.9, 0.73)
Current smoker	65 (57.0)	55 (55.1, 0.84)
UACR (mg/g)	411.0 ± 117.3	416.4 ± 128.2
PCI*	27 (20.6)	23 (20.7, 0.32)
CABG*	21 (16.0)	18 (16.2, 0.25)

*Proportions of PCI, CABG, and PAD were imputed into the sample based on MarketScan prevalence estimates in patients with diabetes and ASCVD.

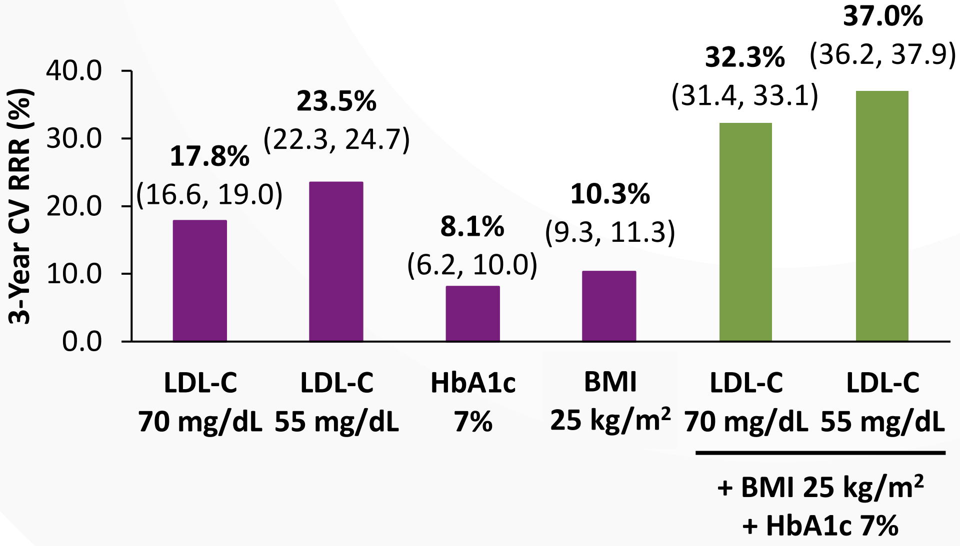
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; eGFR, estimated glomerular filtration rate; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; M, weighted; MI, myocardial infarction; N, representative weighted population; n, sample size; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; SEM, standard error of the mean; UACR, urine albumin-to-creatinine ratio.

Combined Risk Factor Management Results in the Highest Predicted 3-Year CV Risk Reduction

DM + ASCVD



DM + ASCVD + BMI ≥ 27 kg/m²



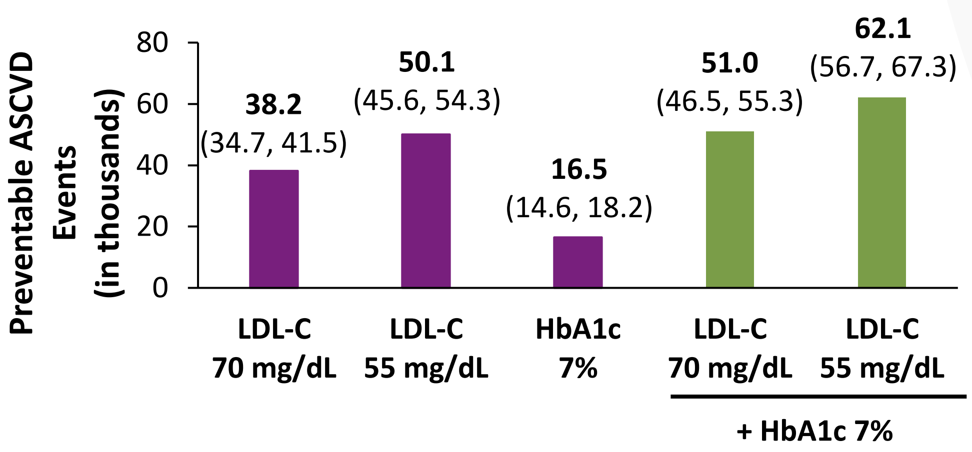
32% predicted RRR for combined management of LDL-C (70 mg/dL), HbA1c, and BMI (37% for LDL-C 55 mg/dL)

Among individual risk factors, management of LDL-C to 55 mg/dL had the highest predicted CV risk reduction at 24% vs 8% for HbA1c and 10% for BMI

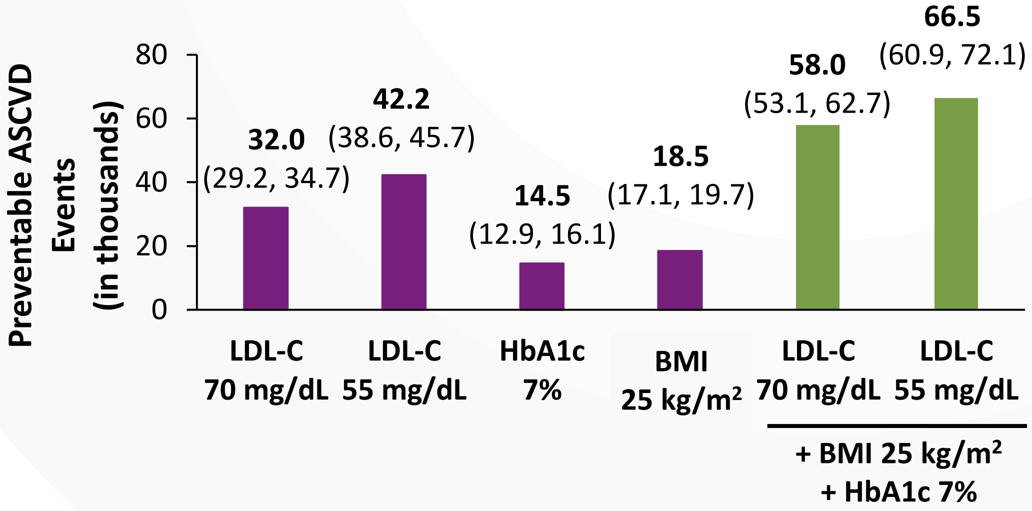
Values in parentheses are 95% confidence intervals.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; CV, cardiovascular; DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol; RRR, relative risk reduction.

Highest Number of 3-Year Preventable ASCVD Events With Combined Risk Factor Management

DM + ASCVD



DM + ASCVD + BMI ≥ 27 kg/m²



58,000 estimated preventable ASCVD events for combined management of LDL-C (70 mg/dL), HbA1c and BMI (66,500 for LDL-C 55 mg/dL)

Among individual risk factors, management of LDL-C to 55 mg/dL resulted in the highest number of preventable ASCVD events at 42,200 vs. 14,500 for HbA1c and 18,500 for BMI

Values in parentheses are 95% confidence intervals.
ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol.

obesityweek®

Strengths and Limitations

- The sample size of our study population is relatively small, but NHANES sampling allows for projections to the representative US population.
- The current analysis was 3-year ASCVD risk prediction based on a TIMI risk score for patients with ASCVD and T2DM, developed and well-validated among four clinical trial cohorts*; however, future studies with longitudinal follow-up data can further verify our findings.
- PCI, CABG, and PAD are components of the TIMI risk score but are absent from NHANES; as such, those prevalences were estimated through MarketScan claims data and randomly imputed in our sample

*SAVOR-TIMI 53, DECLARE-TIMI 58, FOURIER (TIMI 59), and CAMELLIA-TIMI 61.
ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass graft; NHANES, National Health and Nutrition Examination Survey; PAD, peripheral artery disease; PCI, percutaneous infusion; T2DM, type 2 diabetes mellitus; TIMI, thrombolysis in myocardial infarction.

Conclusions

- Among ASCVD and DM patients inadequately controlled for LDL-C and HbA1c, we predicted that about 51,000 – 62,000 recurrent ASCVD events over 3 years could be prevented with guideline achieved control of these measures. It increases to about 58,000 - 67,000 preventable events with the additional control of BMI.
- A substantial portion of residual ASCVD risk in adults with ASCVD and DM can be addressed by optimal control of LDL-C, with further incremental benefit from achieving HbA1c and BMI targets
- Our results demonstrate that comprehensive ASCVD risk control, including LDL-C, HbA1c, and BMI, can have a significant population-wide impact on reducing subsequent ASCVD risk in patients with ASCVD and DM

ASCVD, atherosclerotic cardiovascular disease; BMI, body mass index; DM, diabetes mellitus; HbA1c, hemoglobin A1c; LDL-C, low-density lipoprotein cholesterol.


Q
A