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MACROVASCULAR COMPLICATIONS IN DIABETES (VR ARODA AND A GETANEH, SECTION EDITORS)

Extreme Atherosclerotic Cardiovascular Disease (ASCVD) Risk Recognition

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Abstract

Purpose of Review To distinguish extreme and very high atherosclerotic cardiovascular disease (ASCVD) event risk based on prospective epidemiological studies and clinical trial results.

Recent Findings Clinical practice guidelines have categorized patients with either a history of one or more "clinical ASCVD" events or "coronary heart disease (CHD) risk equivalency" to be at "very high risk" for a recurrence or a first event, respectively. A 20% or greater 10-year ASCVD risk for a composite 3-point "major" atherosclerotic cardiovascular event (MACE) of non-fatal myocardial infarction (MI), non-fatal stroke, or cardiovascular death can serve as an arbitrary definition of those at "very high risk." Exclusion of stroke may underestimate risk of "hard" endpoint 10-year ASCVD risk and addition of other potential endpoints, e.g., hospital admission for unstable angina or revascularization, a 5-point composite MACE, may overinflate the risk definitions and categorization. "Extreme" risk, a descriptor for even higher morbidity and mortality potential, defines a 30% or greater 10-year 3-point MACE (ASCVD) risk. In prospective, epidemiological studies and randomized clinical trial (RCT) participants with an initial acute coronary syndrome (ACS) within several months of entry into the study meet the inclusion criteria assignment for extreme risk. In survivors beyond the first year of an ASCVD event, "extreme" risk persists when one or more comorbidities are present, including diabetes, heart failure (HF), stage 3 or higher chronic kidney disease (CKD), familial hypercholesterolemia (FH), and poorly controlled major risk factors such as hypertension and persistent tobaccoism. "Extreme" risk particularly applies to those with progressive or multiple clinical ASCVD events in the same artery, same arterial bed, or polyvascular sites, including unstable angina and transient ischemic events. Identifying asymptomatic individuals with extensive subclinical ASCVD at "extreme" risk is a challenge, as risk engine assessment may not be adequate; individuals with genetic FH or those with diabetes and Agatston coronary artery calcification (CAC) scores greater than 1000 exemplify such threatening settings and opportunities for aggressive primary prevention.

Summary Heterogeneity exists among individuals at risk for clinical ASCVD events; identifying those at "extreme" risk, a more ominous ASCVD category, associated with greater morbidity and mortality, should prompt the most effective global cardiometabolic risk reduction.

Keywords Atherosclerotic cardiovascular disease (ASCVD) · Major atherosclerotic cardiovascular risk (MACE) · Extreme risk · Very high risk · Multi-morbidities · Secondary prevention

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Abbreviations

AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
ACC	American College Cardiology
AHA	American Heart Association
ASCVD	Atherosclerotic cardiovascular disease
ACS	Acute coronary syndrome
ATP	Adult treatment panel
BP	Blood pressure
CAC	Coronary artery calcification

CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CHD	Coronary heart disease
CHF	Congestive heart failure
CI 95%	Confidence interval
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
eGFR	Estimated glomerular filtration rates
ESC	European Societies of Cardiology
EAS	European Atherosclerosis Society
FH	Familial Hypercholesterolemia
HeFH	Heterozygous familial hypercholesterolemia
HoFH	Homozygous familial hypercholesterolemia
HF	Heart failure
HR	Hazard ratio
HTN	Hypertension
HDL-C	High-density lipoprotein cholesterol
LDL-C	Low-density lipoprotein cholesterol
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MACE	Major adverse cardiovascular events
NCEP	National Cholesterol Education Program
NHLBI	National Heart, Lung, and Blood Institute
NLA	National Lipid Association
NF-MI	Non-fatal myocardial infarction
NNT	Number needed to treat
PAD	Peripheral artery disease
PCSK9	Proprotein convertase subtilisin/kexin type 9
PEP	Primary endpoint
RCTs	Randomized clinical trials
RR	Relative risk
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TIA	Transient ischemic attack
TG	Triglycerides
UA	Unstable angina

Study Acronyms

4-D	Die Deutsche Diabetes Dialyse
AURORA	A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events
CORONA	Controlled Rosuvastatin Multinational Trial in Heart Failure
FOURIER	Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk
FHS	Framingham Heart Study
FOS	Framingham Offspring Study
GISSI-HF	Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-Heart Failure Study
GRACE	Global Registry of Acute Coronary Events
IMPROVE-IT	Improved Reduction of Outcomes: Vytorin Efficacy International Trial
MRFIT	Multiple Risk Factor Intervention Trial
OASIS	Organization to Assess Strategies for Ischemic Syndromes registry
ODYSSEY	Outcomes Trial to determine whether the addition of the PCSK9 antibody alirocumab to intensive statin therapy reduces cardiovascular morbidity and mortality after ACS
PROVE-IT	Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial
REACH	Reduction of Atherothrombosis for Continued Health registry
REVERSAL	Reversal of Atherosclerosis with Aggressive Lipid Lowering trial
RUTHERFORD-2	Reduction of LDL-C with PCSK9 Inhibition in Heterozygous Familial Hypercholesterolemia Disorder Study-2
SHARP	Study of Heart and Renal Protection
SHS	Strong Heart Study
TNT	Treating to New Targets

Introduction

Assigning risk estimates for the development of atherosclerotic cardiovascular disease (ASCVD) and associated clinical events has been an evolving process. Given the burden to humankind of ASCVD, risk estimates have provided clinicians guidance on preventive interventions. In order to routinely apply the multiple proven strategies to prevention, the healthcare provider must understand not only the practicability of ASCVD risk modification but also the diversity of risk factors, the heterogeneity of risks, and the overall magnitude of effect in an individual.

Historical Perspective on the Clinical Recognition of Atherosclerotic Cardiovascular Disease Risk Markers

ASCVD has remained the leading cause of mortality in developed countries since the mid-twentieth century, coincident with improvements in life expectancy [1, 2]. The necessity of the Framingham Heart Study (FHS) was fueled by Franklin D. Roosevelt's history of tobaccoism and severely uncontrolled hypertension (HTN), his subsequent development of coronary artery

disease (CAD), manifested as angina and heart failure, and his premature death by hemorrhagic stroke at age 63 in 1945. In 1948, the FHS [3] began to investigate the causes of CVD with seven initial measurements, including age, total cholesterol, high blood pressure (BP), electrocardiogram (ECG) abnormalities, cigarette smoking, obesity, and hemoglobin level. The term "risk factor" was coined and introduced in 1961 [4]. Over the ensuing years of the FHS, additional data from the Framingham Offspring Study (FOS) initiated in 1971 was collected; cholesterol was recognized as the fundamental causal agent [5] with additional risk factors correlated to the overall ASCVD risk. By the early 1970s, the most important identified risk factors included physical inactivity, impaired glucose tolerance, diabetes, triglycerides, high LDL-C, low HDL-C, isolated systolic BP, atrial fibrillation, left ventricular hypertrophy (LVH), and heart failure [5, 6]. Prospective evaluation has revealed the linear relationship between the number of cigarettes smoked each day and the risk of myocardial infarction (MI) or sudden death [7, 8]. Long-term observations have demonstrated that prolonged cigarette smoking from early adult life tripled age-specific mortality, but cessation at age 50 halved the hazard, and cessation at age 30 eliminated almost all of the risk [7, 8]. Early smoking cessation increased life expectancy, improved quality of life, and reduced healthcare costs. Smoking cessation as a secondary prevention reduced non-fatal MI by 32% and mortality by 36% [9]. As these major coronary heart disease (CHD) risk factors were identified and magnitude of risk quantified, models were developed to predict "10-year" CHD risk [10], refined [11], and further refined in 1998 [12]; and in 1999, the "lifetime" risk of CHD was described [13, 14].

The FHS stratified risks by importance and identified major atherogenic risk factors, by the late 1990s, as dyslipidemia, hypertension, impaired glucose tolerance, hyperuricemia, and elevated fibrinogen. Evidence for the strong positive and independent association of LDL-C with CHD continued to accumulate [15]. Consistent with the risk models for the development of atherosclerosis, the FHS demonstrated that although some risks vary in degree of significance, at any level of cholesterol, coexistent risk factors were additive and influenced the overall risk. With the evaluation and utilization of these risk models, newer improved guidelines were generated from FHS that predicted CHD events [15], and recently more inclusive ASCVD risk equations were derived from new pooled cohorts of several large, racially and geographically diverse cohort studies with adjudicated endpoints for CHD death, non-fatal myocardial infarction, and fatal or non-fatal stroke [16].

Risk Ranking Aids Clinicians in Patient Management

ASCVD risk assessment has been simplified to include only several "major" risk factors: advancing age, diabetes, male gender, cigarette smoking, HTN, elevated total cholesterol, low HDL-C, family history of premature CAD, and only a few risk categories, ranging from low to very high risk, despite long-known risk factors and magnitudes of risk and their significant cumulative effects.[9].

The National Cholesterol Education Program (NCEP) established that the intensity of treatment would be patient risk dependent; higher absolute risk dictates more aggressive treatment [17–19]. The 1988 NCEP Adult Treatment Panel (ATP) [17] utilized the descriptor "high-risk" status to define those patients with a definite MI, or definite myocardial ischemia, such as angina pectoris, or those with two other risks, including history of definite cerebrovascular disease or occlusive peripheral vascular disease, diabetes, severe obesity, low HDL-C, HTN, cigarette smoking, family history of premature CHD, or male sex.

The Adult Treatment Panel II (ATP-II) [18] utilized the descriptor "very high risk" or "highest short-term risk" category to include not only individuals with established CHD at risk for having recurrent CHD events but also individuals with other atherosclerotic diseases, such as peripheral artery disease (PAD) or symptomatic carotid artery disease, and the "high-risk" category included patients without evident CHD who are at high risk because of high blood cholesterol together with multiple other CHD risk factors.

The Adult Treatment Panel III (ATP-III) [19] defined "very high" risk for future events as those at 20% or greater 10-year CHD risk, defined as "hard" CHD events(i.e., MI and CHD death) and included persons with established CHD or those meeting "CHD risk equivalent" criteria. CHD risk equivalents included those with clinical atherosclerosis in other noncoronary arterial beds. The 1-year rate of "major coronary events" ranged between 2.0 and 3.8%; "total mortality" was 2.9% in individuals with PAD, 1.9% CHD mortality in individuals with extensive CAD, and 1.9% "CHD mortality" in individuals that had an abdominal aortic aneurysm repair. CHD risk equivalency was defined also by those with multiple risk factors and a 10-year risk for CHD > 20%, based on the 10-year risk assessment using Framingham Risk scoring described by the ATP III-Framingham Risk Score (FRS) for "hard" CHD events (i.e., MI and CHD death). Having type 2 diabetes mellitus (T2DM) and multiple risks also met criteria for the "very high" 10-year CHD risk > 20% category of "CHD risk equivalency."

"Very High" Risk Implies Impending Events

A first ASCVD event predicts recurrent events that occur in the same artery or same arterial bed or different arterial beds. Preexisting arterial disease symptoms such as angina pectoris and intermittent claudication, or events originating in any arterial bed, such as stroke or transient ischemic attack (TIA), were associated with increased risk of MI, congestive heart failure (CHF), and CAD mortality [20]. Individuals with the greatest likelihood for subsequent atherosclerotic cardiovascular events were those with established CHD. The 1993 ATP II [18] reviewed and recognized epidemiological studies and secondary prevention trials, demonstrating individuals at the "highest risk," "high risk," or "very high risk," terms that were used interchangeably. Individuals post-initial MI were at 5- to 7-fold increased risk for a second MI, including CHD and death compared with the general population. The risk of MI or CHD death is increased by the presence of atherosclerosis in other arterial beds: aorta, limbs, and carotids. Atherosclerotic events in these arterial beds also increased risk for repeat events in the same arterial beds [20]. Individuals with established PAD or carotid disease were at 4- to 6-fold increased risk for CHD events [21]. Individuals with established CHD were at 3- to 4-fold increased risk of stroke and TIA over a 10-year period of follow-up [20]. Post-stroke individuals were at 2- to 3-fold increased risk for MI, angina, and sudden death [20] and at 9-fold increased risk for a second stroke [21]. Relative to those without, individuals with large-vessel PAD were at 3-fold greater risk for all-cause mortality, 6-fold greater risk for all cardiovascular (CV) mortality, 7-fold greater risk for CHD mortality [22], and 2- to 3-fold greater risk for stroke and TIA [23]. Those with severe and symptomatic PAD had a 15-fold greater risk for CV and CHD mortality [22].

Identification of a patient at "very high ASCVD risk," defined as a 2% or greater 1-year risk or a 20% or greater 10-year risk for a "hard event," MI or CHD death [19], prompts aggressive management to decrease the risk of an imminent event that could reduce quality of life and years-of-life.

Thus, historically, the "highest" or "very high" risk cardiovascular category described in clinical practice guidelines [16–19, 24–28] has included individuals with a history of one or more clinical CHD or ASCVD events or those with CHD risk equivalent morbidities including TIA, stroke, PAD, diabetes with ≥2 major risks, or chronic kidney disease (CKD). Identifying the individual at "very high" risk dictates management requiring a multifactorial approach which could be challenging [24].

Aggressive Global Preventive Risk Management Is Obligatory to "Very High"–Risk Patients

Despite survival of a first event, whether by medical therapy or immediate arterial revascularization, the very high–ASCVD risk category implies the presence of diffuse disease and persistent risk, providing the rationale and imperative for aggressive long-term global risk management. Required approaches for risk management include lifestyle management: cholesterol- and triglyceride (TG)–reducing dietary habits including avoidance of excessive alcohol, weight management, physical activity, and tobacco cessation, control of BP and diabetes, pharmaceutical management of atherogenic lipoprotein cholesterol particles, platelet activation, and inflammation and optimal management of CKD, dysrhythmias, heart failure, and other medical conditions that predispose to ASCVD and events including chronic inflammatory disorders [24]. The long-term goal is improvement of life expectancy and quality of life, i.e., delaying mortality without the morbidity associated with recurrent ASCVD events.

Individuals with Type 2 Diabetes and Multiple Risks are "CHD Risk Equivalents" and are at "Very High" ASCVD Risk

The 2001 NCEP ATP-III [19] recognized diabetes mellitus (DM), particularly T2DM, as a CHD risk equivalent due to coincident multiple major risks: hyperglycemia, insulin resistance, metabolic syndrome, and its associated dyslipoproteinemia, and recognized poor prognosis post-MI for recurrent events and mortality. Several studies were reviewed [19] that indicated a 1-year CHD rate of more than 2.0 to 2.5%, even among obese individuals with newly diagnosed T2DM in UKPDS. Of interest, the 1-year CHD rate was just under 2% in leaner individuals with newly diagnosed T2DM. It was also recognized that recent-onset type 1 diabetes mellitus (T1DM) need not necessarily be designated a CHD risk equivalent.

In the Finnish East-West study [29], the 7-year CV mortality was 15.9% among individuals with a prior MI without DM and 15.4% among individuals with DM without prior MI. Extrapolating these 7-year data [29] to 10 years, the "CV death" risk alone was 22.7% and 22%, respectively, consistent with the "very high–risk" category and the designation CHD risk equivalence. The 7-year fatal or non-fatal MI incidence [29] was 18.8% among individuals with a prior MI without DM and 20.2% among individuals with DM without prior MI, extrapolating to 10-year "fatal or non-fatal MI" alone risk 26.9 and 29%, respectively, consistent with "very high risk." The 7-year fatal or non-fatal stroke incidence [29] was 7.2% among individuals with a prior MI without DM and 10.3%

among individuals with DM without prior MI 10.3% and 14.7%, consistent with "high-risk" category. Thus, "risk equivalency" defined by the same risk applied to "CV death," "fatal and non-fatal MI," or "fatal and non-fatal stroke," but in the case of stroke in isolation, 10-year "very high"–risk criteria is not met. Of note, the duration of DM among the cohorts without and with MI was similar at approximately 8 years.

The East-West study [29], as did many other short- and long-term studies [30–38], provided the rationale for treating CV risk factors in individuals with DM without prior MI, as aggressively as in individuals with prior MI without DM and very high 10-year CHD risk > 20% and CHD risk equivalency descriptor [19, 39]. The 18-year prospective population-based CHD mortality follow-up study [34] of these Finnish subjects showed that, relative to patients with prior MI and no DM, the hazard ratio for CHD death, for all subjects with DM, was 0.9 for men and 1.9 for women.

As originally pointed out in the ATP III [19], not all individuals with DM met criteria for CHD risk equivalency, except when projecting risk to age 65. One meta-analysis [40] consisted of 13 studies that included the Finnish East-West study that demonstrated CHD risk equivalency and 12 other studies that did not. The meta-analysis had a total of 45,108 individuals, with mean follow-up of 13.4 years (range 5–25 years) and age range of 25–84 years, and showed that individuals with DM without prior MI had a 43% lower risk of developing "total CHD events" compared with individuals without DM with previous MI. The authors [40] suggested that "public health decisions to initiate cardioprotective drugs in individuals with DM for primary CHD prevention should be based on appropriate individuals' CHD risk estimates rather than a 'blanket' approach of treatment."

Another larger more inclusive review [41] of 25 studies suggested, similar to ATP III [19, 39], that exposure to major risk factors, i.e., metabolic syndrome, older age, longer duration of DM, and, in some, female gender, appeared to confer "CHD risk equivalence." The importance of DM and additional risk factors has been pointed out [39, 42]; while most individuals with DM had a 20% or higher 10-year cumulative incidence, consistent with "very high" risk, it was the presence of multiple risk factors that augments them to the level of "CHD risk equivalency" in the 10-year risk range 25–30%. Thus, there are clearly studies [40–43] demonstrating that some patients with DM without prior MI fall short of "CHD risk equivalency" compared with those patients with preexisting CVD without DM; however, the risk for those with DM alone was also "very high." The likelihood of "CHD equivalency" justifying the "very high"–risk category among patients with DM in the primary prevention setting requires at least 2 or more "major" ASCVD risk factors (Table 1) as suggested by the National Lipid Association (NLA) Recommendations for Patient-Centered Management of Dyslipidemia [27]. The NLA also recognizes that patients with DM are at "very high" ASCVD risk if there is evidence of end organ damage, e.g., increased albumin-to-creatinine ratio (> 30 mg/g), CKD (estimated glomerular filtration rates (eGFR) < 60 mL/min/1.73 m2), or retinopathy.

Larger and longer duration studies demonstrate CHD risk or mortality equivalency [31, 33–36, 45••]. The 2004 ATP III update [46] established factors that supported targeting LDL-C goals to < 70 mg/dL for patients in the "very high"–risk category, defined by those with established CVD plus multiple major risk factors, especially those with diabetes, or severe and poorly controlled risk factors, especially continued cigarette smoking, or multiple risk factors of the metabolic syndrome, defined by non-HDL-C > 130 mg/dL, high TG >200 mg/dL, and low HDL-C < 40 mg/dL, or those with acute coronary syndrome (ACS), based on the Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) (PROVE-IT) trial. CHD risk equivalency is consistent with the high lifetime CHD risk in DM [47, 48]. Recently, an analysis of a large database of more than 3.5 million self-referred participants showed DM was a CHD risk equivalent for PAD and carotid artery stenosis [49].

Recognizing that the "CHD risk equivalency" of DM is indeed dependent on age, the presence of multiple risk factors and longer duration of DM should dictate early and aggressive diagnosis and management of DM and prediabetes and targeting of risk factors to reach appropriate goals for primary prevention of even subclinical ASCVD. Thus, while some patients with diabetes fall short of the "CHD risk equivalency" criteria, their risk remains "high" and with time "very high"; thus, waiting for a duration of diabetes, the development of multiple risks or aging and the development of even subclinical disease and ultimately very high CHD risk before aggressive preventive management would not be prudent.

Type 2 Diabetes Mellitus as ASCVD and Total Mortality Risk Equivalency

It has long been known that patients with diabetes have a higher risk of death post-MI, during the ACS phase, within 30 days, and during longer term follow-up [29–37, 41–43, 45••, 46–51].

The Strong Heart Study (SHS) [42] evaluated 4465 Native Americans, age 45 to 74 years, with DM (48%) and without DM, with and without baseline CHD and CVD, to assess incident non-fatal and fatal CHD and CVD mortality. Vascular risk factors studied included male sex, albuminuria > 300 mg/g creatinine, hypertension ≥ 140/≥90, LDL-C > 100, HDL cholesterol < 40 mg/dL, triglycerides > 150 mg/dL, current cigarette smoking, fibrinogen > 352 mg/dL, and DM duration > 20 years. In individuals with DM and no

Table 1 "Extreme" versus "very high" ASCVD risk recognition: (Percent experiencing 10-year 3-point MACE = CV death or non-fatal MI or non-fatal ischemic stroke)

Very high risk (> 20–30%)	Extreme risk (> 30%)
Clinical ASCVD – Single established clinical ASCVD event, including unstable angina requiring revascularization, i.e., stent or CABG – History of premature clinical ASCVD; male < 55 years of age, female < 65 years of age, in the absence of uncontrolled major risks, DM, or FH	*Clinical ASCVD* – ACS established by hospitalization; applies to < 1 year since the event – Multi-morbidities**, i.e., progressive, or multi-vascular ASCVD; including unstable angina – Established clinical ASCVD* in individuals with (FH (HeFH or HoFH), or DM, or stage ≥ 3b CKD (including hemodialysis), or CHF) – History of premature clinical ASCVD; male < 55 years of age, female < 65 years of age, especially other morbidities are present, e.g., FH, DM, or CKD or chronic inflammatory diseases, or multiple major risk factors that are not controlled, e.g., HTN, or persistent smoking.
Sub-Clinical ASCVD – Severe hypercholesterolemia (LDL-C > 190 mg/dL), especially HeFH or DM or stage CKD ≥ 3b, with ≥ 2 major[§] risk factor(s) or subclinical disease by imaging (CAC > 400 Agatston units)	*Sub-Clinical ASCVD* – Extensive subclinical disease defined by CAC > 1000 Agatston units, especially with DM† – Genetic FH with pathogenic mutation†

ACS (acute coronary syndrome) < 1 year since the event; ASCVD risk defined by #3-point MACE = CV death, non-fatal MI, or non-fatal ischemic stroke

CAC coronary artery calcification, *CKD* chronic kidney disease, *DM* diabetes mellitus, *FH* familial hypercholesterolemia, *Ho* homozygous, *He* heterozygous

*Established clinical ASCVD = historical event in any arterial bed (coronary or peripheral (aortic, carotid, cerebral, lower extremity, or renal))

**Multi-morbidities = clinical ASCVD event involving one vessel in one arterial bed plus other significant morbidity (FH, DM, or CKD polyvascular/multi-vascular events = ≥ 2 events in same arterial bed or vessels in different arterial beds)

[§] Major risk factors include age (> 65 years, male; > 55 years, female), HTN, smoking, low HDL-C, family history premature ASCVD events, ABI < 0.9, elevated Lp(a), hs-CRP > 2, CAC > 100, or drug-naïve common CIMT progression

[†] Unique primary preven5on se6ng of 'extreme' ASCVD risk

(Adaptation and modification of "Extreme Risk" and "Very high risk" categories from *Endocrine Practice*, 23(Supplement 2), Jellinger PS, Handelsman Y, Rosenblit PD, Bloomgarden ZT, Fonseca VA, Garber AJ, et al., 2017 AACE/ACE Guidelines American Association of Clinical Endocrinologists and American College of Endocrinology Guidelines for Management of Dyslipidemia and Prevention of Cardiovascular Disease, 1–87, Copyright (2017), with permission from the American Association of Clinical Endocrinologists) [44••].

history of CHD and 1 or 2 risk factors, the 10-year CHD risk was 1.4-fold higher than those without DM. The 10-year non-fatal and fatal CHD rates increased with the increasing number of risk factors and exceeded 20%, or very high risk; among those with multiple risks, the rates were 21% with 3–4 risks, 35% with 5–6 risks, and 46% with 7–9 risks. Both CHD and CVD mortalities in individuals with DM and multiple risk factors were equivalent to those in individuals with prior CVD or CHD, but no DM. Risk factors for incident CHD common to both groups with and without DM included older age, male sex, prehypertension or hypertension, and elevated LDL-C > 100 mg/dL. However, the 10-year cumulative incidence of fatal CVD, in those individuals with DM and with multiple risk factors, was significantly higher than that in individuals without DM and with previous CVD (34.0 versus 27.6%; $P < 0.03$).

In the 7-year-follow-up, the Finnish East-West (Kuopia-Turku) study [26] discussed above, fatal or non-fatal stroke incidence during follow-up was 10.3% in individuals with DM and no prior MI versus 1.9% in the subjects without DM and no MI. In the 18-year follow-up of the same study [33], the incidence per 1000 patient-years of CHD death was 47.3 in individuals with DM with no prior MI compared with 26.8 in those with a prior MI and no DM, suggesting long-term "CHD mortality" may be a better measure of equivalency. ASCVD that includes non-fatal and fatal stroke risk might also be a better descriptor for CHD risk equivalency.

The Multiple Risk Factor Intervention Trial (MRFIT) Research Group evaluated the impact of diabetes and previous myocardial infarction on long-term survival. The 25-year mortality follow-up of primary screenees in MRFIT [34] demonstrated an age-adjusted CHD death risk, in terms of incidence per 10,000 person-years, of 144.2 for those with DM and no prior CHD but higher at 193.7 for those with prior CHD but no DM; thus, DM fell short of "CHD death risk equivalency." However, "all-cause mortality" was 277.3 and 278, respectively, consistent with "total mortality risk equivalency."

In the Renfrew and Paisley, Scotland, 25-year follow-up survey ($n = 15{,}406$, age 45–64 years), DM was a CHD and "other vascular" mortality risk equivalent [35]. There was no significant difference in other cardiovascular risk factors such as age, smoking, blood pressure, serum cholesterol, BMI, and social class.

The Ontario Registered Persons Database population-based retrospective cohort 2006 study [52] utilized health claims to identify all adults age above 40 with DM (n = 379,003) and without DM (n = 9,018,082), living in Ontario, Canada, from 1994 to 2000. The relation between age and the 6-year incidence of CHD (acute MI or death from any cause) and of CVD (acute MI, stroke, or death from any cause) according to diabetes status and sex was evaluated. There were 104,702 (18.3%) individuals with DM, among the 573,515 individuals with one or more outcome events. Men and women with DM were noted to be approximately 15 years younger than those without DM at the time of an initial acute MI; while absolute rates of CHD or CVD events were lower in younger adults and incidence of events rises with age, young adults, < 40 years of age with DM, had rates of CHD 12–40 times higher than those people without DM. For the outcome of CHD (acute MI or death from any cause), the transition from 10-year risk < 20% (10–19%) to 10-year risk ≥ 20% of CVD took place at about age 49 years for men with DM and 56 years for women with DM, relative to those without DM where 10-year risk ≥ 20% of CVD took place age 61 and 69, respectively. For the outcome of a 3-point CVD (acute MI, stroke, and death from any cause), the transition from 10-year risk < 20% to 10-year risk ≥ 20% of CVD took place at about age 48 years for men with DM and 54 years for women with DM. A broader CVD definition, adding need for revascularization inflated risk, and the transition from 10-year risk < 20% to 10-year risk ≥ 20% of CVD took place at about age 41 years for men with DM and 48 years for women with DM. Using all-cause mortality as a surrogate for CHD-related deaths, similar rates were noted among middle-aged men with either DM or history of AMI alone. The risk of CHD was lower for people with DM alone than for those with a recent history of AMI among men and women younger than 50 years. DM was found to be an ASCVD risk equivalent.

The Emerging Risk Factors Collaboration (ERFC) 2015 analysis [45••] calculated mortality rates and hazard ratios in 91 cohorts for 128,843 deaths among 689,300 participants. The ERFC 2015 analysis also calculated mortality rates and hazard ratios from the UK Biobank of 499,808 participants, with the latest mortality follow-up in November 2013 at 7995 deaths. These analyses demonstrated for individuals age 40 years or older with a single morbidity, either a history DM or MI or stroke, that all-cause mortality rates were comparatively equivalent at 15.6, 16.8, and 16.1 per 1000 person-years, respectively, and 7–8 years-of-life-lost in women and 8–10 years-of-life-lost in men compared with those who were disease-free.

In the Denmark Population study [36] of individuals ≥ 30 years of age (n = 3.3 million), relative to patients with prior MI without DM, patients with DM without prior MI were 3-point major adverse cardiovascular event (MACE) (non-fatal MI, non-fatal stroke, or CV death) risk equivalents. In the Cardiovascular Health study of 5784 older adults above 65 years of age, DM was a CHD mortality equivalent [53]. These large studies provide the rationale for treating CV risk factors of individuals with DM without prior ASCVD, as aggressively as individuals with prior ASCVD without DM over the lifespan. The increase in the number from ≥ 1 to ≥ 2 of major risk factors (Table 1) represents a modification needed to reflect the increased likelihood of "CHD equivalency" among patients with DM in the primary prevention setting in the 2017 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) dyslipidemia [44••].

Individuals With Both Clinical ASCVD and Type 2 Diabetes Are at "Extreme Risk" for Subsequent Events

Regardless of the demonstration of "CHD risk equivalency," comparative epidemiological studies show that cohorts with the multi-morbidity, e.g., DM plus prior ASCVD, have approximately 50 to 100% higher recurrent or initial ASCVD event rates compared with those individuals with a single morbidity, i.e., prior ASCVD without DM or DM without ASCVD [29–38, 41–43, 44••, 45••], justifying partitioning multi-morbidities to "extreme"–risk category and single morbidity to "very high"–risk category, respectively. Deliberating the controversy regarding CHD risk equivalency and contributing factors in their review of 25 population studies, the authors [41] recognized that patients with both diabetes and CAD "are at an extremely high risk of cardiovascular events," and prevention of CAD in patients with DM with statins "has the potential to prevent them from entering the extremely high-risk stratum."

In the large, nearly 700,000 participants, ERFC analysis [45••] above, relative to those without any morbidities, i.e., neither DM nor MI nor stroke, defined as the reference group with a mortality rate at 6.8 per 1000 person-years, individuals with single morbidities, DM alone, or MI without DM or stroke without DM, had nearly identical mortality rates ranging 15.6–16.8 per 1000 person-years with hazard ratios 1.9–2.1. However, the mortality and hazard ratios doubled to 32.0–32.8 per 1000 person-years and 3.5–3.8, respectively, with dual morbidities: MI and DM, stroke and DM, or MI and stroke. Furthermore, the mortality and hazard ratio tripled to 59.5 per 1000 person-years and 6.9, with all three morbidities: DM and MI and stroke, suggesting a "very extreme"–risk category may be needed for triple morbidities. Moreover, the UK Biobank analysis by the ERFC [45••] of 491,424 participants demonstrated similar results among patients with multi-morbidities. While very high-risk "single morbidity" was associated with 7–8 years-of-life-lost in women and 8–10 years-of-life-lost in men compared with those who were disease-free [45••], the "extreme risk" with dual or triple

morbidities was associated with 13–20 years-of-life-lost in women and 16–23 years-of-life-lost in men. From the standpoint of years-of-life-lost after premature events occurring from age 40 for the cohorts described, multi-morbidities were more consistent with "extreme" risk, not single ASCVD events. These data are not consistent with the AACE/ACE dyslipidemia guidelines [44••] categorizing all patients with premature events in the extreme-risk category. Patients with DM and a single ASCVD event [45••] are clearly at "extreme" risk.

In a recent analysis of a large database of more than 3.5 million self-referred participants in the Life Line vascular screening, 10.7% had DM, 5.8% had CHD, 4.4% had PAD, and 3.7% had carotid artery disease. DM was found to be a CHD risk equivalent for PAD and for carotid artery stenosis with odds ratios (OR) of 1.56 and 1.53 compared with 1.69 and 1.72 for individuals with CAD, respectively. Furthermore, participants with comorbid DM and CAD had an especially robust association with PAD (OR 2.75, CI 2.66–2.85) and carotid artery stenosis (OR 2.57, CI 2.49–2.66) [49].

In Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER), participants had inclusion criteria of being ≥ 40 years of age and prior established clinical ASCVD (MI, ischemic stroke, or PAD). The placebo treatment group without DM experienced an 8.4% (505 events in 8264 patients) 3-year Kaplan-Meier rate of the key secondary composite (CV death, MI, or stroke) endpoint, consistent with "very high" extrapolated 10-year 3-point MACE risk of 28%, whereas the placebo treatment group with DM experienced a 12.2% (508 events in 5516 patients) 3-year K-M rate, consistent with the "extreme" extrapolated 10-year ASCVD risk of 40.6%.

Historically, Guidelines Categorized Individuals With Single or Multi-Morbidities Similarly at "Very High" Risk

Despite the greater risk demonstrated in many studies, prior to the 2017 AACE guidelines [44••, 54], clinical practice guidelines, algorithms, or recommendations [16–19, 24–28] historically have categorized those individuals with ASCVD, either a single event or multiple events at the identical highest risk level with identical targeted LDL-C goals. Without doubt, all very high–risk groups deserve to be managed to the most aggressively targeted LDL-C goal, with cardiovascular prevention as ultimate priority; however, considerable residual risk remains for those at extreme risk and may need to be treated even more intensively.

AACE Partitioned the "Very High"–Risk Category, in Recognition of Those at "Extreme" Risk

The 2017 American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE) guidelines for management of dyslipidemia and prevention of atherosclerosis [44••] and the 2017 AACE/ACE comprehensive type 2 DM management algorithm [54], recognizing the above-described discrepancies, defined and emphasized the importance of partitioning the "very high"–risk category to recognize the increased morbidity and mortality of those at "extreme" risk. By consensus, this initial approach by AACE/ACE defined individuals in the "extreme" risk category as those with progressive ASCVD including unstable angina in patients after achieving an LDL-C < 70 mg/dL, established clinical cardiovascular disease in patients with DM, CKD 3/4, or heterozygous familial hypercholesterolemia (HeFH), and history of premature ASCVD (< 55 male, < 65 female). AACE/ACE maintained the "very high" risk classically defined by established or recent hospitalization for ACS, coronary, carotid, or peripheral vascular diseases, diabetes or CKD stages 3 or 4 with one or more risk factor(s) or those with HeFH.

"Extreme"- and "very high"–risk categories can be differentiated and defined in relative terms, whether expressed as hazard ratios, 10-year risk of events, event rates per 100 person-years, or 1000 person-years, or lifetime risk of events or years-of-life-lost. Furthermore, a variety of clinical endpoints have been utilized in epidemiological studies and clinical trials for ASCVD endpoints. In designing clinical trials that are event-driven, the number of specific ASCVD events determine the length of the trial; combining softer endpoints, i.e., hospital admissions for unstable angina, or TIA by example, with harder endpoints, 3-point MACE, will shorten the trial length and also will increase the percent of events over time, thus contributing to exaggerated 10-year ASCVD risk. In population studies and RCTs with added risk components beyond the 3-point hard MACE, i.e., hospitalization for TIA or unstable angina with or without coronary revascularization, or heart failure, or death from any cause, extrapolation to 10-year event rates might provide inflated risk estimates that far exceed 30%.

A 3-point MACE composite of CV death, non-fatal MI, and non-fatal stroke has been the primary endpoint (PEP) of several recent randomized cardiovascular outcome trials, although some primary endpoints include additional components. AACE/ACE has limited the categorization utilizing 10-year 3-point MACE (CV death or non-fatal MI or non-fatal stroke), considered the top 3 "hard endpoints" that are frequently utilized as primary or secondary endpoints in randomized clinical trials.

Thus, a cohort with established ASCVD without DM, or a cohort with DM and major risks (CHD risk equivalents), has been defined by the "very high" risk or a 10-year ASCVD risk > 20%. AACE/ACE limits the "very high"–risk category to a 10-year 3-point MACE (CV death or non-fatal MI or non-fatal stroke) risk of 20–30% from individuals. A cohort with established ASCVD plus specific comorbidities, i.e., DM or familial hypercholesterolemia (FH) or CKD, or a cohort with progressive, i.e., multiple, ASCVD events, in the same or different arterial beds is at "extreme" risk and defined as a 10-year 3-point MACE risk > 30%. In its guidelines, AACE suggested that patients at extreme risk warranted an even lower targeted LDL-C goal < 55 mg/dL, instead of < 70 mg/dL.

Improved Reduction of Outcomes: Vytorin Efficacy International Trial Demonstrated Incremental Lowering of LDL-C and Improved ASCVD Outcomes

The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT), [55] post-ACS, at a median 6-year follow-up, add-on ezetimibe to moderate dose simvastatin demonstrated a CVD benefit [ARR 2.0%; number needed-to-treat (NNT), 50; p = 0.016]. The in-trial 1-year mean levels of LDL-C, non-HDL-C, and Apo B were lowered to 53.2 mg/dL, 77.2 mg/dL, and 70.3 mg/dL, in the simvastatin + ezetimibe arm relative to 69.9 mg/dL, 97.1 mg/dL, and 81.3 mg/dL, respectively, in the simvastatin alone arm. But the significant benefit was limited to those with DM (ARR, 5.5%; NNT, 18; p=0.001) and did not extend to those without DM (ARR 0.6%, NNT 167, p=0.471). This may be a problematic issue when targeting LDL-C, since LDL-C is deceptively low in states of insulin resistance, such as diabetes. In such states there is an unfavorable discordance-associated with an increase in LDL particle numbers (LDL-P), [56] and, also an associated increase in the more ominous atherogenic triglyceride-rich lipoprotein cholesterol remnants [57]. In the absence of assessment of LDL-P or Apo B [58] or non-HDL-C [59], the oversimplified surrogate, it may be an imperative to have a lower LDL-C goal for individuals with the unfavorable discordance seen in states of insulin resistance. Furthermore, despite ACS event rates meeting 'extreme' criteria, the categorization and setting of atherogenic lipoprotein cholesterol marker goals in the 2017 AACE/ACE dyslipidemia guidelines was problematic, since the ACS patients without diabetes in IMPROVE-IT were relatively unresponsive, in terms of ASCVD event reduction

"Extreme" Risk in Other Populations

In addition to individuals with comorbidities of DM and ASCVD, several other populations meet criteria for the extreme-risk category, where the 10-year risk for 3-point MACE is greater than 30% or the 1-year risk exceeds 3%; differentiated from the "very high" that carries a 20–30% 10-year or a 2–3% 1-year risk.

"Extreme"–Risk Individuals Include Those With Acute Coronary Syndrome

An acute coronary syndrome (ACS) is associated with significantly elevated immediate, subsequent, and recurrent ASCVD events; especially during hospitalization, within 30 days, and up to 1-year post-ACS, after which the rate of CV events is attenuated [31, 50, 55, 60–66].

In the Organization to Assess Strategies for Ischemic Syndromes (OASIS) registry [31] of 8016 global individuals post-ACS, the 2-year incidence of death, in individuals with no prior CVD and no DM, was 6.9%, with prior history of CVD and no DM was 12.8%, with DM and no prior CVD was 13.0%, and with both prior CVD and DM was 20.3%. Extrapolating these 2-year OASIS data to 10-years, the mortality rises to 34.5%, 64%, 65%, and 102%, respectively, a likely overestimation since recurrent rates are greatest in the first year. Thus, individuals with recurrent events, already at the "very high–risk" category and with targeted atherogenic cholesterol "goal" of LDL-C < 70 mg/dL, may remain at extreme risk despite treatment with a statin. In the PROVE-IT [63] trial, the 2-year rate of the 2-point MACE composite, death from any cause or MI, was 16% in the pravastatin 40 mg group and 12.9% in the atorvastatin 80 mg group. The extrapolated 10-year death or MI risk was 80% and 64.5%, respectively. Furthermore, in an exploratory post hoc analysis of the PROVE-IT trial [64], participants experienced within the short 2-year trial not only the prespecified first event after the initial ACS qualifying event but also 340 and 275 additional MACE in the pravastatin and atorvastatin groups, respectively. Thus, limiting the 10-year risk to the first PEP event designated in a randomized clinical trial underestimates the significance of extreme risk in ACS individuals.

In the IMPROVE-IT [55], the PEP was a composite 5-point MACE CV death, major coronary event (non-fatal myocardial infarction, documented unstable angina requiring hospital admission, or coronary revascularization occurring at least 30 days after randomization event, or non-fatal stroke at 7 years was 32.7% in the simvastatin-ezetimibe group compared with 34.7% in the simvastatin-monotherapy group (HR 0.936; CI 0.89 to 0.99; $P = 0.016$)). In the analysis of total PEP events (CV death, MI, stroke, unstable angina [UA] leading to

hospitalization, coronary revascularization > 30 days post-randomization) during a median 6-year follow, 56% were first events and 44% subsequent events, again demonstrating the extreme risk associated with ACS [65]. The 3-point MACE (CV death, MI, or stroke) at 7 years was 20.4% in the simvastatin-ezetimibe group compared with 22.7% in the simvastatin-monotherapy group (HR 0.936; CI 0.89 to 0.99; $P = 0.016$). The extrapolated 10-year 3-point composite MACE risk for the control arm was 32.4% consistent with extreme risk.

ODYSSEY OUTCOMES [66] was a multicenter, randomized, double-blind, placebo-controlled trial involving 18,924 patients who had an ACS 1 to 12 months earlier. Patients received statin therapy at a high-intensity dose or at the maximum tolerated dose and qualified for the study if after 2 weeks the lipid demonstrated an LDL-C ≥ 70 mg/dL or a non-HDL-C ≥ 100 mg/dL. Patients were randomly allocated alirocumab subcutaneously at a dose of 75 mg (9462 patients) or matching placebo (9462 patients) every 2 weeks, with a mean follow-up of 2.8 years. The PEP composite (death from CHD, non-fatal MI, fatal or non-fatal ischemic stroke, or unstable angina requiring hospitalization) was significantly ($P < 0.001$) reduced by 15%.

The mean 2.8-year follow-up percent incidence for the control (placebo) endpoints of CV death or non-fatal MI or ischemic stroke was 2.9%, 7.6%, and 1.6%, respectively for this estimated 3-point composite MACE of 11.1% or an extrapolated 10-year 3-point composite MACE estimated at 41.7% consistent with "extreme" risk. In the alirocumab-allocated arm, the percent incidence for these components was reduced to 2.5%, 6.6%, and 1.2%, respectively.

The "on-treatment analysis" [66] demonstrated that in ACS patients, despite a baseline LDL-C of 91 mg/dL and nearly all (88.8%) of these ACS patients receiving background high-intensity atorvastatin or rosuvastatin, treatment with alirocumab resulted in a mean LDL-C of 38 mg/dL at 4 months, 42 mg/dL at 1 year, and additional drift upwards to 53 mg/dL at 4 years (mean participant follow-up 2.8 years), a numerical goal consistent with the 2017 ACE guidelines/ACE goal for "extreme"–risk category. Thus, alirocumab, possessing the necessary LDL-lowering potency and CV risk reduction efficacy in ODYSSEY OUTCOMES dispels the need to demonstrate progressive disease and achieved an LDL-C < 70 mg/dL, before instituting more aggressive therapy, at least in the extreme ACS setting, to reach the "extreme" category goal of < 55 mg/dL, new evidence supporting modification of the AACE/ACE guideline.

In a multicenter prospective cohort study in Switzerland [67] between 2009 and 2013, 4534 patients with ACS were screened for familial hypercholesterolemia (FH) and all were observed for 1-year risk of first recurrent coronary events defined as coronary death or myocardial infarction. The 1-year death rate was 3.4%, including 2.3% for fatal MI, and the 1-year non-fatal MI rate was 2.5%; combined fatal and non-fatal MI rate was 4.8%. The prevalence of FH in the entire cohort was 1.6 to 5.5% depending on the FH definition. Multivariable adjustment, including age, demonstrated that the hazard ratios for recurrent CHD death or non-fatal MI were 2.43 to 3.53 for the FH patients, with FH definition–dependent mean age for the index ACS at 50–56 years, relative to mean age of 66 years for those without FH. Thus, while the entire cohort of patients post-ACS meets criteria for "extreme" recurrent event risk, the relatively smaller population, represented by FH, that suffered premature index ACS events was at "very extreme" recurrent event risk.

The relocation of ACS into the extreme-risk category is a modification of the 2017 AACE/ACE dyslipidemia guidelines (Table 1).

In addition to ASCVD among patients with DM, and recent ACS, other morbidities also meet criteria for "extreme" risk, including a history of clinical ASCVD with multiple ASCVD bed involvement [37, 48, 49, 62, 68–72] and clinical ASCVD with CKD [38, 73, 74].

Polyvascular Disease or Multiple ASCVD Beds Exemplify Extreme Risk

It is long known from the pre-statin era that survival was dependent on the extent of disease including the extent and number of diseased coronary arteries. In the Coronary Artery Surgery Study (CASS), among the 24,959 patients enrolled between 1975 and 1979, there was a variable spectrum of survival risk from moderate to extreme risk [72].

Polyvascular (aortoiliac, femoral-popliteal, and carotid) disease burden versus CAD alone predicted increased 3-point MACE or in-hospital mortality after undergoing coronary angioplasty; the in-hospital mortality was 0.7% if no other vascular bed involvement, 2.0% with one additional vascular bed involved, and 2.6% if greater than or equal to 2 vascular beds. Beyond 6 months post-angioplasty, the incidence of mortality was 7% if no other vascular bed involvement, 15% with one additional vascular bed involved, and 22% if 2 other vascular beds experienced MACE [68].

The influence of polyvascular disease was examined in a review [69] of several cohorts including the Reduction of Atherothrombosis for Continued Health (REACH) Registry and Global Registry of Acute Coronary Events (GRACE), and the ARIC cohort that prospectively evaluated rates of MI, CV death, stroke or TIA, from the time of acute hospitalization up to 10 years, and stratified by the number of affected vascular beds. Approximately, 15 to 30% with atherosclerosis present with disease in multi-vessel beds and experience significantly greater rates of adverse CV events than patients with single vessel disease.

GRACE [62] included 48,418 individuals in-hospital and 32,735 individuals in 6-month follow up analysis. Compared with those who had ACS, only individuals with ACS and PAD and/or stroke had higher rates of death, MI, or stroke, both in-hospital and at 6 months and even higher among individuals with ACS, PAD, and stroke. Among patients enrolled in the REACH Registry, the 1-year rate of 3-point MACE increased from 4.1% for patients with single vessel disease to 9.2% for patients with disease in all three—coronary, carotid, lower extremity—vessels.

Another analysis of the REACH Registry [37] illustrated the heterogeneity of risk by single versus polyvascular bed involvement, time since an ischemic event, and diabetes status, in its evaluation of 3-point MACE risk at 4-year follow-up. Relative to individuals with risk factors only and a hazard rate of 9.1%, those with no prior ischemic event but with recognized single vessel disease and those with polyvascular disease had a hazard rate of 11.5% and 17.7%, respectively. Among those with a prior ischemic event as single vessel disease had a hazard rate of 15.7% while those with polyvascular disease had a hazard rate of 25%. The REACH Registry multivariable analysis modeling demonstrated that a history of prior event predicted future events, and if the event occurred within the prior year, significantly greater risk was predicted, and the presence of either diabetes or polyvascular disease distinguished those as an "extremely high-risk population."

The Further Cardiovascular Outcomes Research with PCSK9 Inhibition in Subjects with Elevated Risk (FOURIER) [70] is a double-blind, placebo-controlled trial involving 27,564 patients with ASCVD and LDL-C ≥ 70 mg/dL, randomized to evolocumab (either 140 mg every 2 weeks or 420 mg monthly) or matching placebo with a median follow-up of 2.2 years. Among the placebo patients in FOURIER [71], recognizing that 37% had DM, those with a history of single arterial bed involvement as MI or stroke morbidity, 3-point composite MACE (CV death, MI, or stroke) occurred in 7.6%, for a 10-year extrapolated MACE risk of 34.5%, while those with PAD, that, in reality, is 2-extremity arterial beds disease, 10.3% or 10-year extrapolated MACE 46.8%. Those with polyvascular disease, either MI or stroke and PAD, the 2.2-year MACE was 14.9% for an extrapolated 10-year MACE risk of 67.7%, consistent with "extreme" risk.

Patients With Chronic Kidney Disease Associated With the Usual Major Risks Are "Very High" ASCVD Risk: Those Patients With CKD With Clinical ASCVD, or Diabetes, Are at Extreme Risk

Chronic kidney disease (CKD) incidence correlates linearly with the number of "metabolic syndrome" components [72]. The multivariable-adjusted HRs of 1.30 and 1.37 for CKD were statistically significant for metabolic syndrome using the ATP-III and the International Diabetes Federation (IDF) definitions, respectively. Thus, prediabetes, dysglycemia, hypertension, dyslipidemia, and obesity are associated causally in 2/3 of individuals with CKD.

Recent dyslipidemia guidelines from the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS) recommend that individuals with eGFR (in mL/min/1.73 m^2) of 60–30 mL/min/1.73 m2 should be classified as "high-risk" 10-year CHD risk 10–20% and with eGFR < 30 mL/min/1.73 m2 as "very high–risk" 10-year CHD risk > 20% [28]. Recommendations from the National Lipid Association (NLA) [27] classify individuals with stage 3B or 4 CKD (eGFR 15–44) in the "high-risk" category and individuals with stage 5 CKD or on hemodialysis in the "very high"–risk category. Furthermore, individuals with both DM (T1DM or T2DM) and stage 3 (eGFR < 60) are at very high risk.

In the Study of Heart and Renal Protection (SHARP) [74], 9270 eligible individuals had CKD, 3023 (33%) were on dialysis, and no known history of either MI or coronary revascularization, and 1393 (15%) had a history of vascular disease, defined as history of angina, stroke, or peripheral vascular disease. Twenty-three percent had both CKD and DM. Individuals were randomized to receive simvastatin 20 mg and ezetimibe 10 mg versus placebo. At the median duration follow-up of 4.9 years, 11.3% allocated to simvastatin-ezetimibe versus 13.4% allocated to placebo experienced the PEP outcome, 4-point MACE composite (non-fatal MI or coronary death, non-hemorrhagic stroke, or arterial revascularization procedure) corresponding to a statistically significant 17% relative risk (RR) reduction (HR 0.83, 0.74–0.94; $P = 0.0021$). The extrapolated 10-year 4-point MACE for the cohort allocated to the placebo group was 27.3% consistent with a rate in the "very high"–risk category. The rate of the 4-point MACE at 4.9-year follow-up in the placebo was proportional to the degree of CKD: 6.8% with eGFR > 60, 10.4% with eGFR 30–60, 12.7% with eGFR > 15–30, 13.3% with eGFR < 15%, and 16.5% if on dialysis. CKD ≥ stage 3 is associated with greater than 20% 10-year risk rendering CKD as an ASCVD risk equivalent [74–76] and at "very high–risk" level. In the context of this review, however, the PEP outcome for those with both CKD and previous vascular disease was greater; 23.5% in the simvastatin-ezetimibe and 25.2% in the placebo group. For those with both CKD and DM, the rate was 18.3% on simvastatin-ezetimibe and 22.5% for the placebo. The extrapolated 10-year 4-point MACE rates were 51% and 46% ("extreme" risk) in the CKD and previous vascular diseases, and CKD and DM placebo groups, respectively.

In the Die Deutsche Diabetes Dialyse (4-D) [77], 1255 individuals with T2DM and on hemodialysis for less than 2 years, were randomized to placebo or atorvastatin 20 mg. After a median 4-year follow-up, 226/619 (37%) in the atorvastatin group versus 243/636 (38%) experienced the primary composite 3-

point MACE endpoint. The extrapolated extreme 10-year 3-point MACE risk was 93% for the placebo group. In A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) [78], 2776 individuals on hemodialysis were randomized to placebo or rosuvastatin 10 mg. After a median 3.8-year follow-up, 396/1389 (28.5%) in the rosuvastatin group versus 408/1384 (29.5%) in the placebo group experienced the primary composite 3-point MACE. The extrapolated extreme 10-year 3-point MACE risk was 78% for the AURORA placebo group.

That SHARP, 4-D, and AURORA failed to demonstrate that lipid-lowering reduced mortality or ASCVD events therapy in dialysis patients may be due to a variety of factors [73, 77, 78], including a failure to reduce targeted atherogenic cholesterol to low enough levels required in this extreme-risk setting.

Heart Failure as an Extreme Mortality Risk and Extreme ASCVD Risk in CORONA

In the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico Heart Failure (GISSI-HF) trial [79], the effect of rosuvastatin in patients with chronic heart failure (CHF) was evaluated. In this randomized, double-blind, placebo-controlled trial, individuals aged 18 years or older with New York Heart Association (NYHA) class II–IV CHF, irrespective of cause and left ventricular ejection fraction, were randomly assigned to rosuvastatin 10 mg daily (n = 2285) or placebo (n = 2289). Primary endpoints were time to death and time to death or admission to hospital for cardiovascular reasons. Follow-up was for 3.9 years. There was no difference in death (28% versus 29%, adjusted HR 1.00 [95.5% CI 0.898–1.122], p = 0·943) or admission to hospital for cardiovascular diseases (57% versus 56%, adjusted HR 1.01 [99% CI 0.908–1.112], P = 0·903) [75]. An estimated, 3.1% had fatal and non-fatal MI and 2.9% fatal and non-fatal stroke; these rates were relatively low compared with death due to arrhythmia 8.0%, or heart failure admission 27.7%, or total mortality 28.1%, or death due to any cardiovascular reason 21.3%. The GISSI-HF trial results reflect the "extreme" mortality risk of heart failure, irrespective of the heart failure cause.

In contrast to the GISSI-HF trial, Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) [80] randomized 5011, at least 60 years of age, with chronic, symptomatic, NYHA class II, III, or IV systolic heart failure of "ischemic cause" to receive 10 mg of rosuvastatin or placebo. During a median follow-up of 32.8 months, the PEP outcome 3-point composite MACE, CV death, non-fatal MI, or non-fatal stroke occurred in 692 (11.4%) in the rosuvastatin group and 732 (12.3%) in the placebo group (HR 0.92; 95% [CI] 0.83 to 1.02; P = 0.12); the difference in risk of death between the groups was also not statistically significant (HR 0.95; 95% CI 0.86 to 1.05; P = 0.31). The extrapolated 10-year 3-point MACE was 45.1% reflecting the "extreme" ASCVD risk of heart failure. That both GISSI-HF and CORONA failed to demonstrate that statin therapy reduced mortality or ASCVD events, respectively, might be due to a variety of factors [79, 80], including a failure to reduce targeted atherogenic cholesterol to low enough levels required of this extreme-risk setting. Recognizing CHF as an "extreme risk" is an important modification of the AACE/ACE dyslipidemia guidelines (Table 1).

Atherogenic Lipoprotein Cholesterol Thresholds or Goals that Limit Disease Progression

"Extreme" ASCVD risk is demonstrated in secondary prevention population in epidemiological studies and randomized clinical trials. In the setting of primary prevention, selected populations of asymptomatic individuals may also be at extreme risk. The goals of management have been diverse. Historically, goal-oriented guidelines or recommendations have targeted atherogenic cholesterol markers (LDL-C, non-HDL-C, Apo B, or LDL-P) as a one and the same threshold and numerical goal below which one aims [17–19, 24–28, 44••, 54, 58, 81–83]. The 2013 ACC/AHA [84] guideline was level 1A randomized clinical trial strictly evidence-based in nature. The guideline identified groups by ASCVD risk levels that would benefit from statin use, recommended percent LDL-C reductions needed, based on risk, and eliminated numerical thresholds or goals for atherogenic cholesterol markers. Soon after this guideline was published, atherogenic cholesterol, e.g., LDL-C, level exposure burden as a fundamental causal risk, deserving a targeted goal for reduced outcomes, was amply and exquisitely described in 2014 [85]. In 2016 and 2017, thresholds for treatment, percent LDL-C reduction, and, coincidentally, "considerations" for targeting LDL-C below the threshold as a concept was reintroduced [86, 87].

Selected recent recommendations/guidelines have described the upper limits of targeted LDL-C goals to be at or near 100 mg/dL even in low-risk individuals [29, 30], with lifestyle changes recommended to achieve such goals and not necessarily initiating pharmacologic agents. The ADA defined an LDL-C > 100 mg/dL as a "major risk" in managing patients with DM [88].

A pooled analysis of five intravascular ultrasound (IVUS) studies [89] of individuals with CAD (n = 2237) has demonstrated more extensive disease and more rapid progression in individuals with DM compared with those without DM. Importantly, more progression than regression occurred in individuals with DM at an LDL-C > 80 mg/dL, compared with those without DM, and regression exceeded progression for individuals with DM when LDL-C was < 80 mg/dL but less so than in individuals without DM. In the Study of Coronary Atheroma by

Intravascular Ultrasound: Effect of Rosuvastatin Versus Atorvastatin (SATURN) [90], after 2 years of high-intensity statin therapy, percent atheroma volume (PAV) regression was less in those with DM, compared with those without DM, when LDL-C levels were > 70 mg/dL but similar when LDL-C levels were ≤ 70 mg/dL on treatment. In addition, the supplementary data suggests progression of disease is recognized at LDL values > 85 mg/dL in individuals without DM and > 65 mg/dL in individuals with DM and with a slightly downward trend with lower on-treatment LDL-C only in the individuals with DM.

Can Asymptomatic Individuals Be at 10-Year Extreme ASCVD Risk Exceeding 30%?

Severe Hypercholesterolemia Levels Especially With Recognized Genetic Variants Qualify as an Extreme Risk

Since atherogenic cholesterol is fundamental to the atherosclerosis process, individuals with familial hypercholesterolemia exemplify extreme risk. Homozygotes (HoFH) with estimated prevalence of 1 to 6 per million [91], demonstrate angiographically detectable CAD before the age of 20 years, beginning on average at 13 years of age [92], and untreated rarely living beyond 30 years of age [89]. Heterozygote familial hypercholesterolemia (HeFH) is a genetic disorder due to mutations in the LDL receptor gene or apolipoprotein B gene or PCSK9 genes that cause reduced clearance of LDL-C and lifelong elevated levels of LDL-C usually > 190 mg/dL and causing premature ASCVD. Heterozygotes (HeFH) with estimated prevalence of 1 to 2 per 500 have angiographically detectable coronary disease at 17 and 25 years of age in males and females, respectively [92], suffering premature ASCVD events [93, 94] even in the absence of other major risks [93]. The cumulative probabilities of a first attack of ischemic heart disease before age 60 among women and men with clinical HeFH in various studies [94] were 85.4% and 57.5% in the UK, 52% and 31.8% in the USA, 35% and 20% in Japan, and 83% and 70% in Norway. The mean age of onset of ischemic heart disease in males and females with HeFH was 40 and 50 years in Quebec and 44.2 and 53.1 years in France.

It has been pointed out [95] that, while 7% of the adults in the USA have severe hypercholesterolemia defined by an LDL-C > 190 mg/dL, simply having an LDL-C > 190 mg/dL does not mean one has genetic FH. Among 26,025 participants from 7 case-control studies and 11,908 from 5 cohort studies, 1386 (6.7%) had LDL cholesterol ≥ 190 mg/dL, but only 24 (1.7%) carried an FH mutation (LDLR, APOB, or PCSK9). In individuals without FH, those with LDL-C levels ≥ 190 mg/dL had a 6-fold higher risk for CAD compared with those with LDL-C levels < 130 mg/dL. Those with LDL-C levels ≥ 190 mg/dL with a FH pathogenic variant exhibited a 22-fold increased risk for CAD [95]. Thus, the presence of a FH pathogenic variant increases CAD risk > 3-fold at the same elevated LDL-C level, attributed to greater lifelong exposure to elevated LDL-C levels. From the 12-week evolocumab safety and efficacy study, RUTHERFORD-2 trial population [96] of statin-treated individuals with FH, the "10-year" CV risk and "lifetime" CV risk were estimated [97]. CV events were defined as acute coronary syndrome, ischemic stroke, and heart failure and CV mortality. The predicted overall 10-year CV risk of one or more events was 45%. The risk was higher in secondary prevention (61%) than in primary prevention (32%), the latter meeting criteria for "extreme" risk. The predicted lifetime risk ranged from 86 (primary prevention) to 91% (secondary prevention). Despite not yet experiencing a clinical ASCVD event, genetic FH with pathogenic mutation should be recognized as "extreme" risk (Table 1) and represents a modification of the AACE/ACE dyslipidemia guidelines.

Elevated Coronary Artery Calcium Score

The 2010 ACCF/AHA guideline [98] for assessment of CV risk in asymptomatic adults recognizes that coronary artery calcium (CAC) measured by computed tomography (CT) is a dependable marker of coronary artery atherosclerosis and the CAC Agatston score is an excellent predictor of ASCVD events in individuals with and without DM. Furthermore, the guideline recognizes that some asymptomatic individuals are categorized by FRS as having a 10-year ASCVD risk of 10–20% ("high risk"), a CAC score of 300, or greater would reclassify them to a 10-year event rate ≥ 20%, consistent with the "very high"–risk ASCVD category. Survival curves for 10,377 asymptomatic individuals [99] found that the 3-year mortality for a CAC score of > 400 was 5%, extrapolated to 10-year the mortality increased to 17% or "high risk"; if the CAC score was > 1000, the 3-year mortality was 9.5%, extrapolated to 10-year the risk increases to 32%, meeting criteria for "extreme" risk for this single very hard endpoint component of 3-point MACE. Among the 903 individuals with DM, CAC score of > 400 was associated with a 9% 3-year mortality that extrapolates to 10-year risk of 30% just meeting criteria for "extreme" risk. When the CAC score was > 1000, 3-year mortality was 16% or a 10-year mortality of 53%, or "extreme" risk. No doubt these figures describing solely the endpoint of "mortality" would be considerably higher if non-fatal MI or stroke were components of a 3-point MACE composite.

The Screening for Heart Attack Prevention and Education (SHAPE) Task Force published a practice guideline for cardiovascular screening in the asymptomatic at-risk population based on detection and treatment of those with subclinical atherosclerosis among all asymptomatic men 45–75 years of age and asymptomatic women 55–75 years of age [100], at a time when existing guidelines did not recognize severe non-obstructive coronary atherosclerosis as a CHD risk equivalent even though most

heart attacks originate from non-obstructive coronary plaques. Very high risk was defined by the 2006 SHAPE guideline by either a ≥ 50% stenotic plaque or a CAC Agatston score > 100 along with a carotid intimal media thickness > 90th percentile or a CAC score ≥ 400. A summary of 14,856 patients in 5 large prospective randomized studies [101], 3 with 3-point composite PEP CHD death, MI, and revascularization and 2 with CHD death and MI, demonstrated that a CAC score > 400 is a "CHD equivalent," with 10-year event rates exceeding 20% (22.5–28.6%) in asymptomatic patients. A CAC score exceeding 1000 had a 10-year event rate 37%, consistent with "extreme" risk. Clearly, subclinical disease identified by CAC Agatston score > 400 Agatston units represents very high risk (Table 1). Extensive subclinical disease defined by CAC > 1000 Agatston units, not limited to but especially among those with DM, despite not yet experiencing a clinical ASCVD event, should be recognized as "extreme" risk (Table 1) and represents a modification of the 2017 AACE/ACE dyslipidemia guidelines.

Future risk evaluations aimed at identifying and characterizing subclinical disease early such as increased progression rates assessed by CAC sequential score, coronary computed tomography angiography (CCTA), 3-D carotid ultrasound, biomarkers, or combinations may also assist in identification of subclinical ASCVD in primary prevention individuals also at "extreme" risk.

"Extreme" ASCVD Risk Distinguishes the More Ominous Stratification of 10-Year 3-Point Composite (Non-Fatal MI, Ischemic Stroke or CV Death) Risk Exceeding 30%

"Extreme" risk categorization, established in the 2017 AACE/ACE dyslipidemia guidelines [44••], partitioned the "very high"–risk category, to convey the recognition of patients with the greatest incidence of ASCVD events. Thus, rather than describe all patients with one or more clinical ASCVD events at "very high" risk and a 10-year ASCVD risk > 20%, a partition was made to distinguish those identified by examination of prospective epidemiological studies and randomized clinical trials with the more ominous stratification 10-year ASCVD risk > 30%.

"Very high" risk applies to those with 10-year risk of 3-point MACE > 20–30% and comprises those with a history of a single ASCVD event, i.e., non-progressive disease, or to those individuals with "CHD risk equivalents," including DM, FH, CKD stage 3 or 4, and most often also possessing one or more major risk factors.

"Extreme" risk is identified by the presence of multiple morbidities, comprising those patients with either 2 or more clinical ASCVD events, e.g., progressive events, or a history of a single clinical ASCVD event and in addition possessed of another "very high"–risk morbidity or "CHD risk equivalency" and the 10-year 3-point composite (CV death, non-fatal MI, or ischemic stroke (ASCVD)) risk exceeds 30%.

Recognizing "extreme" risk and "very high" risk heterogeneity, the former possessing more ominous risk and greater post-management residual risk, can guide clinicians in further treatment decisions: use of more potent approaches for achievement of lower targeted biomarker goals, e.g., utilizing add-on non-statin therapies, not only ezetimibe [63, 74] but also PCSK9 inhibitors [66, 70, 71, 86, 87, 102, 103] to further reduce atherogenic cholesterol particle numbers.

AHA/ACC/Multi-Specialty 2018 Guideline Distinguishes "ASCVD Not at Very High Risk" from "Very High-risk ASCVD"

The 2018 ACC/AHA/multi-society clinical practice guideline on the Management of Blood Cholesterol [104] represents an update of the 2013 ACC/AHA cholesterol guideline [84], with noted improvements of a targeted LDL-C ≥ 70 mg/dL as a "threshold" for statin initiation and additional therapeutic-lowering with non-statin drugs, as suggested in the 2016 [87] and 2017 [103] ACC Expert Consensus Decision Pathways on Non-statin Considerations. Clinical ASCVD is defined as ACS, those with history of MI, stable or unstable angina or coronary or other arterial revascularization, stroke, TIA, or PAD including aortic aneurysm; all of atherosclerotic origin. The 10-year risk for a first hard ASCVD event remains defined as the risk of developing a first ASCVD event, defined as non-fatal myocardial infarction or CHD death, or fatal or non-fatal stroke, over a 10-year period among people free from ASCVD at the beginning of the period [16]. The 10-year risk for ASCVD is categorized as low risk (< 5%), borderline risk (5 to < 7.5%), intermediate risk (7.5 to <20%), and high risk (≥ 20%).

As in the 2017 AACE/ACE guidelines, [44••] 2018 AHA/ACC/Multi-Society guidelines [104] have updated to similarly recognize a necessary partition of patients with ASCVD and distinguish those with a history of "multiple major ASCVD Events" or a single major clinical ASCVD event plus multiple high-risk conditions, from a single relatively more stable ASCVD, described by the nomenclature "ASCVD not at very high risk." Thus, at least in part, the difference in the 2 guidelines, appears to be semantics; the 2017 AACE/ACE nomenclature defines those at the highest risk as "extreme" risk, and the 2018 AHA/ACC/Multi-Specialty nomenclature defines those at the highest risk as "very high" risk. The 2017 AACE/ACE dyslipidemia guidelines [44••, 54] nomenclature recognized "high risk" as a 10-20% 10-year

3-point MACE risk defined by either the presence of ≥2 risk factors, or DM or CKD stage 3,4 without other major risk factors. The "very high risk" category recognizes those with a 20-30% 10-year ASCVD risk, defined by history of a single ASCVD event, including an ACS, or in the absence of a history of prior ASCVD event by a single important very high-risk morbidity or condition that is consistent with CHD or ASCVD risk equivalency, including heterozygous familial hypercholesterolemia (HeFH) or CKD stage 3 or 4, or DM, either with ≥2 risks. The 2017 AACE/ACE guidelines consider a large list of risk factors similar to, but not as extensive as, the 'high-risk conditions' and 'risk-enhancing factors' utilized in the 2018 AHA/ACC/Multi-specialty guidelines in determining ASCVD risk categorization.

The 2017 AACE/ACE distinguishes multi-morbidities and premature ASCVD events as "extreme-risk" category, a more ominous setting, defined by a 10-year ASCVD risk exceeding 30%, demonstrated in epidemiological studies and clinical trials, with the consensus caveat that lipid-lowering therapy had not yet demonstrated benefit. The results of the landmark IMPROVE-IT trial [55] demonstrated the evidence-based benefit when lowering LDL-C to 53.7 mg/dL, supporting the concept that even lower than < 70 mg/dL is better for extreme risk ACS patients and the support for a change in the guideline goal for targeted LDL-C to < 55 mg/dL. However, while a 2% ARR and NNT of 50 overall was demonstrated, the cohort with ACS without DM showed little or no benefit from reduction of LDL-C to < 55 mg/dL, while those with DM had a 5.5% ARR with 18 as NNT. Therefore, due to the lack of response for patients without diabetes, despite the entire cohort experiencing evidence-based statistically significant risk reduction at 7 years and the control "simvastatin-monotherapy group" experiencing a prespecified 3-point MACE (CV death, MI, stroke) of 31.7%, the AACE/ACE dyslipidemia writing committee, by consensus, took a departure from level 1A evidence base and chose to keep "ACS patients," in general, in the "very high–risk" category. Patients with DM and ASCVD, included DM with ACS, were categorized at "extreme" risk.

Thus, "extreme" risk represents an extended partition of the "very high"–risk category and suggests that significantly more aggressive global risk management, including atherogenic cholesterol lowering might reduce the multi-morbidity-associated years-of-life-lost, and history of CHF.

Conclusion

In summary, there are compelling prospective epidemiological and clinical trial data, in support of the "extreme"–risk category, where the 10-year 3-point MACE (CV death, non-fatal MI, and non-fatal stroke) exceeds 30%. The "very high"–risk category is limited to a 10-year 3-point MACE risk > 20–30%, high risk at 10–20%, moderate risk at 5–10%, and low risk < 5%.

Independent of response in lipid-lowering therapeutic trials and including updated evidence-based clinical trial data, modifications of the original 2017 ACE/ACE guidelines, defining the "extreme"–risk category (Table 1), include individuals with a history of:

1. An ACS event and up to 1 year from the event, or
2. Multi-morbidities defined by a single established "clinical ASCVD" events plus any single or multiple additional morbidities, e.g., those individuals with DM, or CKD ≥ 3, including those on dialysis, or CHF, at least of ischemic origin, or genetic predisposing FH or chronic inflammatory disorders
3. Multi-morbidities defined by 2 or more clinical ASCVD events, i.e., progressive disease, in the same or multiple arterial beds or
4. Premature established clinical ASCVD prior to age 45 in males or 55 years of age in females, in particular those with FH, or DM, or CKD ≥ 3 or severe uncontrolled "major risks" HTN or persistent smoking, or history of severe hypercholesterolemia, including those with genetic FH or other predisposing genetic inflammatory disorders
5. Diabetes in the primary prevention setting that are otherwise asymptomatic but have extensive subclinical atherosclerosis defined by a coronary artery calcification (CAC) score exceeding 1000 Agatston units
6. Individuals in the primary prevention setting that are otherwise asymptomatic with proven genetic variant mutations consistent with familial hypercholesterolemia (FH), known to contribute to premature ASCVD events

The "very high"–risk category comprises patients with a history of:

1. A single established clinical ASCVD at ≥ 1 year from the event, including angina requiring revascularization, i.e., stent or CABG
2. CHD risk equivalents including HeFH or DM or stage CKD 3 or 4, along with ≥ 1 major risk factor(s) or subclinical ASCVD defined by CAC > 300 Agatston units

Refinements in the extreme-risk category definition are in a dynamic mode, to be continuously updated with better understanding of the impact of ASCVD multi-morbidities, TG-rich lipoprotein remnant cholesterol, elevated lipoprotein(a), elevated C-reactive protein, exaggerated major risks, and chronic inflammatory

comorbidities are explored, along with findings on atherosclerosis imaging studies such as coronary artery calcification, coronary CT angiography, or other 3-D vascular bed imaging techniques.

Recognition by clinicians in practice of individuals at ominous "extreme" risk is likely to result in increased sensitivity to utilize the most aggressive approaches and attain the most success in risk reduction. Ultimately, managing those at extreme and very high risk requires approaches that embrace global risk reduction, including the lowering of the fundamental targeted atherogenic cholesterol particle, i.e., LDL-C, goals, at least for those at extreme risk, that approach zero. This may be especially important for patients with stage 5 CKD on hemodialysis and those with CHF of ischemia origin, to prevent ischemic events in whom the limited LDL-lowering in trials to date failed to reduce ASCVD events and mortality. In addition, management of "extreme" risk will likely yield the greatest benefit once pharmacological advances permit superior reduction of the other causal atherogenic lipoprotein cholesterol particles, i.e., TG-rich lipoprotein remnant cholesterol and lipoprotein(a), that contribute to considerable residual risk.

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Compliance with Ethical Standards

Conflict of Interest

12-month 1/1/18-12/31/18 disclosure

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