Introduction

- How is ASCVD risk assessed?

- What are the benefits and disadvantages of the various available risk assessment tools?

- Is metabolic syndrome a stronger predictor of CV risk compared to CV risk scoring tools?

- How do emerging risk markers further refine risk stratification?

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease.

Cardiovascular Disease Risk

- Worldwide, CVD is the leading cause of disability and premature death

- Primary prevention depends on the accurate estimation of individual CV risk

- CVD risk prediction tools estimate the probability of having a CV event within a defined timeframe, based upon the levels or presence of known risk factors

CVD = cardiovascular disease.

Lippi G, et al. *Journal of Medical Systems* (2018) 42:68:1-5. https://doi.org/10.1007/s10916-018-0925-6.

CV Risk Assessment

- CV risk is estimated as either absolute, relative, lifetime, or recurrent
  - **Absolute risk**: CV risk prediction for a given future period (5-10 years)[1]
  - **Relative risk**: Ratio of CVD risk to a low-risk age- and sex-matched comparison group[1]
  - **Lifetime risk:** Risk prediction beyond 10 years[1]
  - **Recurrent risk**: The chance that a cancer that has been treated will occur[2]
- An internationally agreed-upon guideline does not exist[1]

CVD = cardiovascular disease.

1. Ruwanpathirana T, et al. *Cardiovascular Therapeutics.* (2015)33:62–70.
2. National Cancer Institute website: https://www.cancer.gov/publications/dictionaries/genetics-dictionary/def/recurrence-risk.

CV Risk Assessment: Review of Risk Calculators

AACE Guidelines: CV Risk Assessment

- The 10-year risk of a coronary event (high, intermediate, or low) should be determined by detailed assessment using 1 or more of the following tools:
  - Framingham Risk Score
  - MESA 10-year ASCVD Risk with Coronary Artery Calcification Calculator
  - Reynolds Risk Score, which includes hsCRP and family history of premature ASCVD
  - UKPDS risk engine to calculate ASCVD risk in individuals with T2D

- When HDL-C is >60 mg/dL, 1 risk factor should be subtracted from an individual's overall risk profile

- A classification of elevated TG should be incorporated into risk assessments to aid in treatment decisions

- Special attention should be given to assessing women by determining the 10-year risk of a coronary event using the Reynolds Risk Score or the Framingham Risk Assessment Tool

AACE = American Association of Clinical Endocrinologists;
ASCVD = atherosclerotic cardiovascular disease;
HDL-C = high-density lipoprotein cholesterol; hsCRP = high-sensitivity CRP;
MESA = Multi-Ethnic Study of Atherosclerosis; TG=triglycerides; T2D=type 2 diabetes.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497.

CV Risk Assessment: Risk Calculators

CV Risk Assessment Calculator	Method
Framingham[1]	Calculates 10-year risk of heart attack for adults 20 years of age or older who do not have heart disease or diabetes
MESA[1]	Calculates 10-year ASCVD risk with coronary artery calcification
Reynold's Risk Score[1]	Calculates 10-year risk of heart attack, CVA or other major heart disease in healthy people without diabetes
UKPDS[1]	Calculates risk of ASCVD in persons with T2D; this risk is up to 3x greater than that of the general population

ASCVD = atherosclerotic cardiovascular disease;
CVA = cerebrovascular accident; MESA = Multi-Ethnic Study of
Atherosclerosis; T2D = type 2 diabetes; TG = triglycerides;
UKPDS = United Kingdom Prospective Diabetes Study.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497.

ESC/EAS: CV Risk Assessment

- The ESC/EAS 2016 Guidelines recommend the Systemic Coronary Risk Estimation tool (SCORE) because it is based on large representative European cohort datasets.

- SCORE estimates 10-year cumulative risk of first fatal atherosclerotic event, whether a heart attack, stroke, or other occlusive arterial disease including sudden cardiac death.

- It facilitates risk estimation in apparent healthy persons with no documented CVD.

ESC/EAS: CV Risk Assessment

- In high- and very high-risk persons, aggressive risk reduction is recommended[1]

- In all others (moderate or low risk), apply the SCORE risk assessment tool[2]

- SCORE is based on a large European cohort and can be re-calibrated for other populations; a low-risk version is also available[2]

- **Evaluates 10-year risk of fatal CVD[2]**

- Only applicable to individuals aged 45-65 years; criteria include: age, gender, total cholesterol, systolic BP[2]

BP = blood pressure; CKD = chronic kidney disease; CVD=cardiovascular disease; ESC/EAS = European Society of Cardiology/European Atherosclerosis Society; FH = familial hypercholesterolemia; GFR = glomerular filtration rate; LDL-C = low-density lipoprotein-cholesterol; SCORE = systematic coronary risk evaluation; T2D = type 2 diabetes.

1. Kanji M, et al. *Ann Intern Med*. (2016) 165:713-722.
2. Catapano A, et al. *European Heart Journal*. (2016) 37:2999–3058.

Risk Category[2] (LDL-C Goal)	Risk factors/10-year risk[2]
Very High (LDL-C <70 mg/dL)	• Documented CVD, clinical or unequivocal on imaging • T2D with target organ damage or + 1 risk factor • Severe CKD (GFR <30 mL/min/1.73 m2). • SCORE ≥10%
High (LDL-C <100 mg/dL)	• Elevated **1** risk factor • Chol >310 mg/dL (e.g. in FH) or BP ≥180/110 mmHg. • T2D • Moderate CKD (GFR 30–59) • SCORE ≥5% and <10%
Moderate (LDL-C <115 mg/dL)	SCORE ≥1% and <5%
Low (LDL-C <115 mg/dL)	SCORE <1%

CV Risk Scores Limitations

Score	Framingham
• Predicts the risk of dying from ASCVD (mortality), disregarding non-fatal events (morbidity)	• Underestimates risk in: patients >70 years of age, primary hyperlipidemias (FH, FCHL), indigenous populations, metabolic syndrome
• Does not predict the natural history of ASCVD, but rather the end result after using all available means to keep patients with ASCVD alive	• May overestimate risk in countries with a low CVD mortality rate and vice versa
• Not applicable in patients older than 65 years of age	• Population-specific, only applicable to Caucasians
• Risk thresholds are arbitrary	• 10-year risk (lifetime risk more useful)
• May overestimate risk in countries with low CVD mortality rates, and vice versa	• Not all traditional factors are included (eg, obesity)
• Recalibration to target population necessary	• Socioeconomic aspects, family history, and ethnicity not included
• May underestimate risk in patients with diabetes, central obesity, and/or family history of premature CVD	• Assumes constant effect of risk factors

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease;
FCHL = familial combined hyperlipidemia FH = familial hypercholesterolemia.

Hobbs F, et al. *Q J Med.* (2010) 103:727–739.

Cardiovascular Risk Assessment: Role of Metabolic Syndrome

What Is the Metabolic Syndrome?

- A clustering of risk factors for CVD and T2D[1]
  - Metabolic syndrome doubles ASCVD risk and confers 5 times greater risk for T2D
- Worldwide prevalence:[1] ~35-40%
- A premorbid condition that includes:
  - Arterial hypertension[1]
  - Atherogenic dyslipidemia (hypertriglyceridemia and low HDL-C)[1]
  - Elevated fasting plasma glucose[2]
  - Central obesity[1,2]
- A clinical construct that aids in selecting patients for preventive measures to reduce risk[1,2]
- Multiple definitions and questions regarding its validity and utility in clinical practice[2]

ASCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease;
HDL-C = high-density lipoprotein cholesterol; T2D = type 2 diabetes.

1. Alberti K, et al. *AHA Journals.* (2009) 120:1640-1645.
   DOI: 10.1161/CIRCULATIONAHA.109.192644.
2. Cameron A. *Maturitas.* (2010) 65:117–121.

Metabolic Syndrome: 2009 Harmonized Definition

2009 Harmonized Definition ≥3 of the following:[1]	
Obesity	Waist circumference (geographic- and ethnic-specific)
Dyslipidemia	HDL-C <40 mg/dL (men); <50 mg/dL (women) TG ≥150 mg/dL or treated
Hyperglycemia	FPG ≥100 mg/dL or treated
Hypertension	SBP ≥130 mm hg, DBP ≥85 mm hg or treated

Until 2009, the clinical usefulness of a metabolic syndrome diagnosis was partially hampered by the use of multiple definitions. Then, 6 groups released a joint interim statement regarding the development of a single, standardized definition to harmonize the various criteria: International Diabetes Federation, American Heart Association, NHLBI, World Heart Federation, International Atherosclerosis Society, and International Association for the Study of Obesity.[1,2.]

DBP = diastolic blood pressure; FPG = fasting plasma glucose;
HDL-C = high-density lipoprotein cholesterol; NHLBI = National Heart,
Lung, and Blood Institute; SBP = systolic blood pressure; TG = triglyceride.

1. Alberti K, et al. *AHAJournals.* (2009) 120:1640-1645. DOI: 10.1161/CIRCULATIONAHA.109.192644.
2. Sampson S, et al. *Endocrinol Metab Clin N Am.* (2014) 43:1–23.

Metabolic Syndrome: Predicting CV Risk

- CV risk scores are the best evidence-based tools for absolute risk estimation, however they have their limitations.

- Metabolic syndrome focuses attention on a clustering of health problems that increase future diabetes risk, and it is a better predictor of T2D than CVD.

- The integration of both into a cardiometabolic framework that merges their strengths in one model makes sense from a clinical, pathophysiologic, and public health standpoint.

CV = cardiovascular disease; CVD = cardiovascular disease; T2D = type 2 diabetes.

Cardiovascular Disease Risk Assessment: Refining Risk Stratification

Refining Risk Stratification: Additional CVD Risk Markers

Biomarkers	Subclinical CVD Markers
hsCRP1,2*	CAC1,2*
Fibrinogen1	ABI2
NT-proBNP3	Carotid IMT1,2*
Troponin4	EKG
Cystatin C5	
Homocysteine1*	
Lipoprotein a1,2*	
Lp-PLA2 1*	
Albumin1,2	
MPO6	

* These risk markers are discussed in subsequent slides

ABI = ankle-brachial index; apo = apolipoprotein;
CAC = Coronary artery calcification;
CVD = cardiovascular disease;
EKG = Electrocardiography; hsCRP = high-sensitivity C-reactive protein; IMT = intima-media thickness;
Lp-PLA2 = lipoprotein-associated phospholipase;
MPO = Myeloperoxidase; NT-proBNP = N-terminal pro b-type natriuretic peptide.

1. Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497; 2. Grundy S, et al. J *American Coll Cardiol*. https://doi.org/10.1016/j.jacc.2018.11.003;
3. Panagopoulou V, et al. *Curr Top Med Chem*. 2013;13(2):82-94. 4. Blankenberg S, et al. *Eur Heart J*. 2016;37(30):2428-2437; 5. Taglieri N, et al. *Clin Chem*. 2009 Nov;55(11):1932-1943; 6. Schindhelm RK, et al. *Clin Chem*. 2009;55(8):1462-1470.

Refining Risk Stratification: AACE Guidelines

Risk Marker	AACE Recommendation
High sensitivity C-reactive protein (hsCRP)	Use to stratify ASCVD risk in individuals with a standard risk assessment that is borderline, or in those with an intermediate or a high risk with an LDL-C concentration <130 mg/dL
Lipoprotein-associated phospholipase A_2 (Lp-PLA$_2$)	Measure to further stratify ASCVD risk, especially in the presence of hsCRP elevation as some studies have demonstrated greater specificity than hsCRP
Coronary artery calcification (CAC)	Measure to determine the need for more aggressive treatment strategies; has been shown to be of high predictive value
Carotid intima media thickness (CIMT)	May be considered to refine risk stratification to define need for more aggressive ASCVD preventative strategies

Routine measurement of homocysteine, uric acid, plasminogen activator inhibitor-1, or other inflammatory markers is not recommended because the benefit is not sufficiently proven

AACE = American Association of Clinical Endocrinologists;
ASCVD = atherosclerotic cardiovascular disease;
LDL-C = low-density lipoprotein cholesterol.

Jellinger P, et al. *Endocr Practice*. (2017) 23(4):479-497.
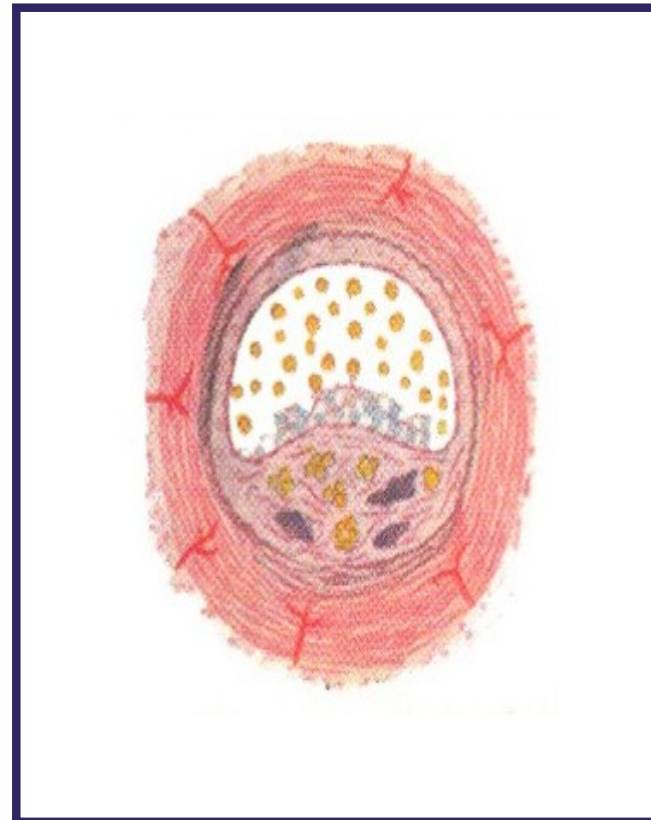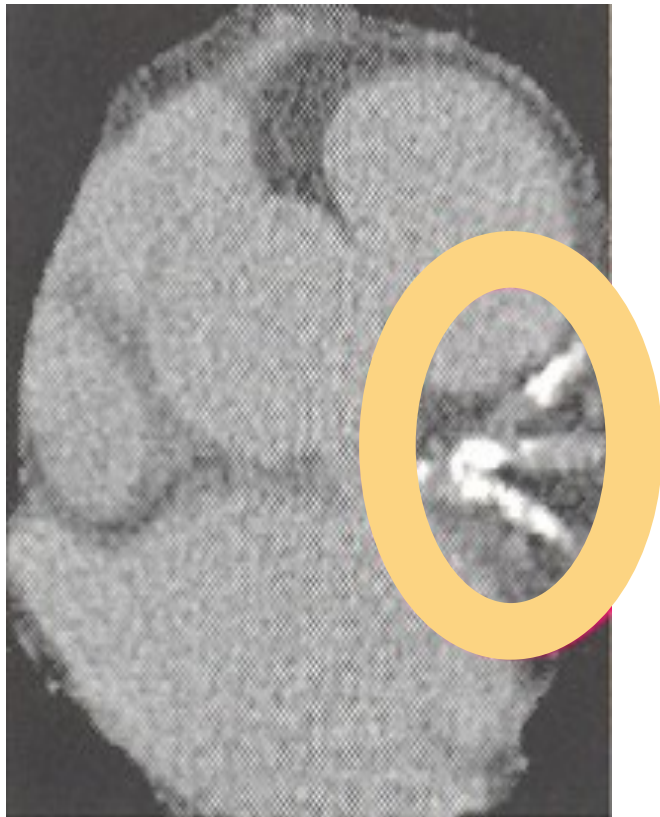
Coronary Artery Calcification
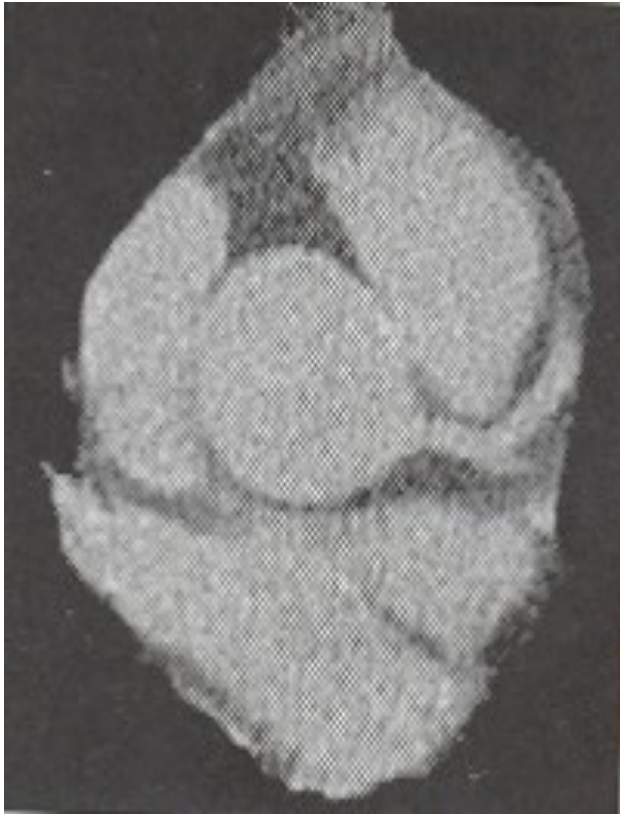
- CAC is a noninvasive measure of atherosclerosis that has emerged as an adjunct to standard ASCVD risk factors[1]
- Recognized by the AHA as a surrogate marker for CAD[1]
- The presence of CAC correlates strongly with coronary atherosclerosis and is an important predictor of ASCVD risk[1]

AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; CAC = coronary artery calcification; CAD = coronary artery disease.

Jellinger P, et al. *Endocr Practice.* (2017) 23:2-87.

Coronary Artery Calcification

Value of Coronary Artery Calcium Scanning:
The Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research (EISNER) Trial

Compared with no scanning, randomization to CAC scanning was associated with superior coronary artery disease risk-factor control without increasing downstream medical testing.

Among patients who received CACS scanning, the composite Framingham Risk Score (FRS) at 4 years increased from baseline, among the scan subjects with a zero CAC score, but FRS decreased among subjects with elevated CAC scores.

Parameters	No CACS Scanning	CACS Score 0	CACS Score >400	*P*-value*
Change in LDL-C	-11 mg/dL	-12 mg/dL	-29 mg/dL	<0.001
Change in SBP	-5 mmHg	-4 mmHg	-9 mmHg	<0.001
Exercise	36%	32%	47%	0.03
New Lipid Rx	25%	19%	65%	<0.001
New BP Rx	18%	20%	46%	<0.001
New ASA Rx	7%	5%	21%	<0.001
Lipid Adherence	86%	80%	88%	0.04

ASA = atrial septal abnormalities; BP = blood pressure; CAC = Coronary Artery Calcium; HDL-C=high-density lipoprotein cholesterol; LDL-C=low-density lipoprotein cholesterol; Rx=medical prescription; SBP=systolic blood pressure.

*P-values are for CACS=0 vs CACS >400

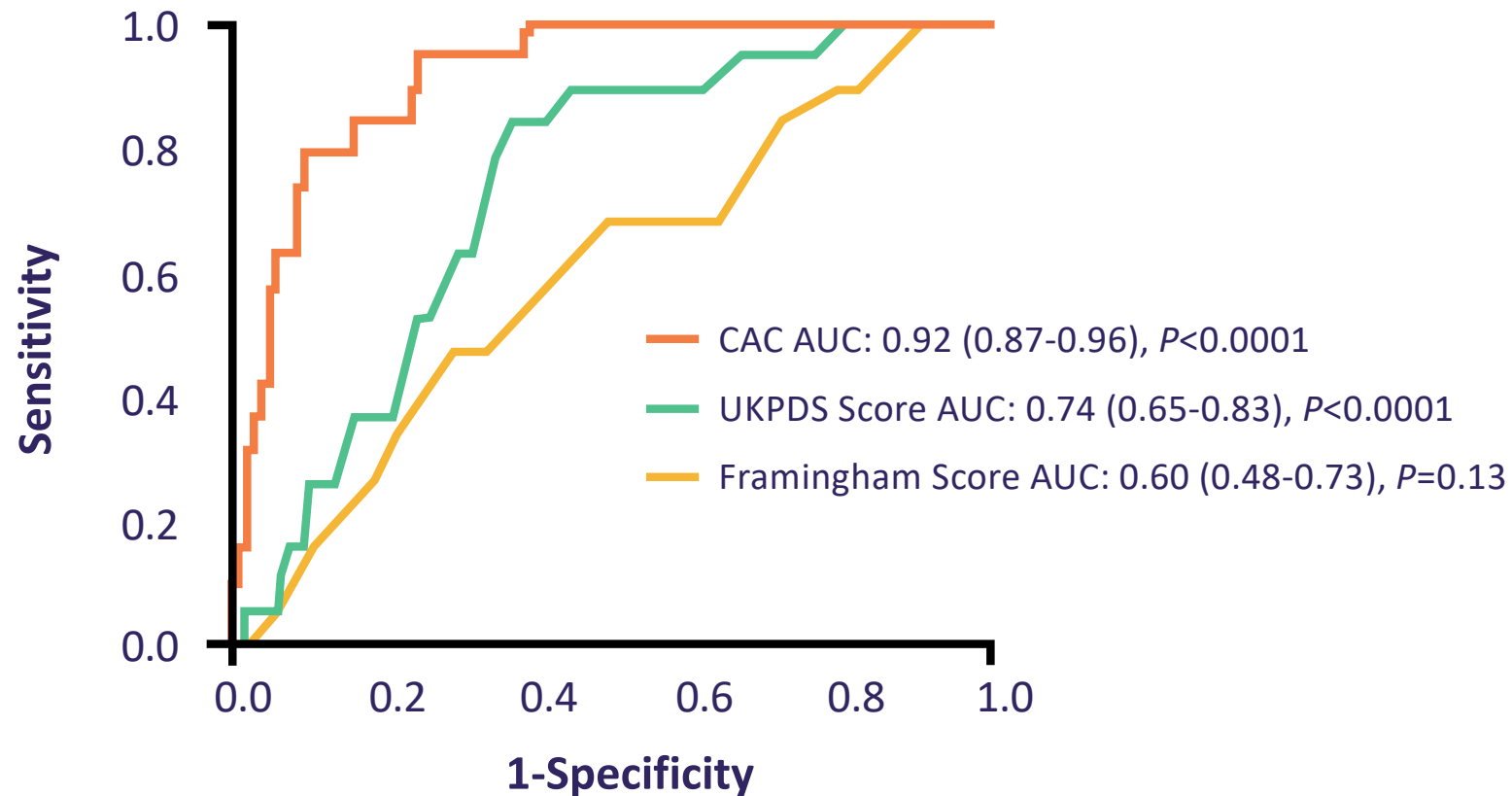Rozanski A, et al. *J Am Coll Cardiol. (*2011) 57(15):1622-1632.

Coronary Artery Calcium in Multi-Ethnic Study of Atherosclerosis (MESA)

- **MESA 10-year outcomes showed that CAC is an independent risk factor for CVD[2,3]**
  - CAC predicts CVD risk in patients with or without traditional risk factors and in patients with family history of premature CHD[2,4,5]
  - CAC was the strongest predictor of CVD in low-risk patients2[1,2,6]

- **The MESA risk score uses traditional risk factors and CAC to predict 10-year CHD risk[7]**
  - The incorporation of CAC into this risk score has improved risk prediction

CAC = coronary artery calcification; CHD = coronary heart disease; CVD = cardiovascular disease; MESA = Multi-Ethnic Study of Atherosclerosis.

1. Bild DE, et al. *Am J Epidemiol.* 2002;156:871-881; 2. Blaha MJ, et al. *Circulation.* 2016;133:849-858; 3. Yeboah J, et al. *J Am Coll Cardiol.* (2016) 67:139-147.
4. Patel J, et al. *Circ Cardiovasc Imaging.* (2015) 8:e003186; 5. Silverman MG, et al. *Eur Heart J.* (2014) 35:2232-2241; 6. Joshi PH, et al. *Atherosclerosis.* (2016) 246:367-373; 7. McClelland RL, et al. *J Am Coll Cardiol. (*2015) 66:1643-1653.

Comparing the Value of FRS, UKPDS Risk Engine, and CAC Score for Predicting CV Events

CAC AUC: 0.92 (0.87-0.96), *P*<0.0001

UKPDS Score AUC: 0.74 (0.65-0.83), *P*<0.0001

Framingham Score AUC: 0.60 (0.48-0.73), *P*=0.13

AUC = appropriate use criteria; CAC = coronary artery calcification;
CV = cardiovascular; FRS = Framingham Risk Score;
UKPDS = United Kingdom Prospective Diabetes Study.

Anand DV, et al. *European Heart Journal.* (2006) 27:713–721.

38