TABLE 1 Description of Included Studies

Study	Design	PY of Study	Rate per 100,000 PY (95% CI)
Thompson et al. JAMA 1982;247:2535–8	Retrospective	76,368	13.09 (4.98 to 21.21)
Waller et al. Clin Cardiol 1992;15:851–8	Prospective	829,089	1.69 (0.80 to 2.57)
Fuller et al. Med Sci Sports Exerc 1997;29:1131–8	Prospective	16,845	0.33 (0.27 to 0.40)
Maron et al. J Am Coll Cardiol 1998;32:1881–4	Retrospective	651,695	0.75 (-1.33 to 2.82)
Van Camp et al. Med Sci Sports Exerc 1995;27:641–7	Retrospective	30,093,579	0.46 (-0.06 to 0.98)
Durakovic et al. J Sports Med Phys Fitness 2005;45:532–6	Retrospective	3,930,000	0.15 (0.03 to 0.27)
Corrado et al. JAMA 2006;296:1593–601	Prospective	1,954,382	1.87 (1.38 to 2.37)
Chevalier et al. Eur J Cardiovasc Prev Rehabil 2009;16:365–70	Prospective	317,205	1.26 (0.03 to 2.50)
Drezner et al. Circulation 2009;120:518–25	Prospective	64,200,000	1.59 (1.03 to 2.14)
Maron et al. Circulation 2009;119:1085–92	Prospective	1,239,112	0.61 (0.55 to 0.67)
Holst et al. Heart Rhythm 2010;7:1365–71	Retrospective	1,239,112	1.21 (0.60 to 1.82)
Solberg et al. Eur J Cardiovasc Prev Rehabil 2010;17:337–41	Retrospective	2,597,204	0.85 (0.49 to 1.20)
Marijon et al. Circulation 2011;124:672–81	Prospective	169,742,000	0.33 (0.31 to 0.36)
Steinvil et al. J Am Coll Cardiol 2011;57:1291–6	Retrospective	923,076	2.38 (1.39 to 3.38)
Roberts and Stovitz. J Am Coll Cardiol 2013;62:1298–301	Retrospective	1,666,509	0.24 (0.00 to 0.48)
Toresdahl et al. Heart Rhythm 2014;11:1190–4	Prospective	1,577,366	0.13 (-0.05 to 0.30)
Risgaard et al. Heart Rhythm 2014;11:1673–81	Prospective	3,035,521	1.45 (1.02 to 1.88)
Harmon et al. Circulation 2015;132:10–9	Prospective	4,242,519	1.86 (1.45 to 2.27)
Grani et al. Eur J Prev Cardiol 2016;23:1228–36	Retrospective	24,392,760	0.59 (0.50 to 0.69)
Bohm et al. Eur J Prev Cardiol 2016;23:649–56	Prospective	120,000,000	0.09 (0.07 to 0.11)
Harmon et al. Mayo Clin Proc 2016;91:1493–502	Retrospective	6,974,640	0.99 (0.76 to 1.22)
Overall		437,156,081	0.72 (0.58 to 0.86)

Test for heterogeneity: $I^2 = 97.4\%$; $Q = 791.88$; $p < 0.001$.
CI = confidence intervals; PY = person years.

possible explanation for this is our inclusion of only English language literature (i.e., mainly from North America and Europe).

In conclusion, in a meta-analysis of observational studies incorporating 1,994 SrSCD over >430 million PY, the incidence of SrSCD is low at 0.72 per 100,000 PY (1 death per 138,889 PY).

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Appropriate Referrals of Angiography Despite High Prevalence of Normal Coronary Arteries or Nonobstructive CAD

National registry data indicate that approximately 60% of patients referred for invasive coronary angiography (ICA) have normal coronary arteries (NCA) or non-obstructive coronary artery disease (CAD) (1). Some have suggested that the rather low prevalence of

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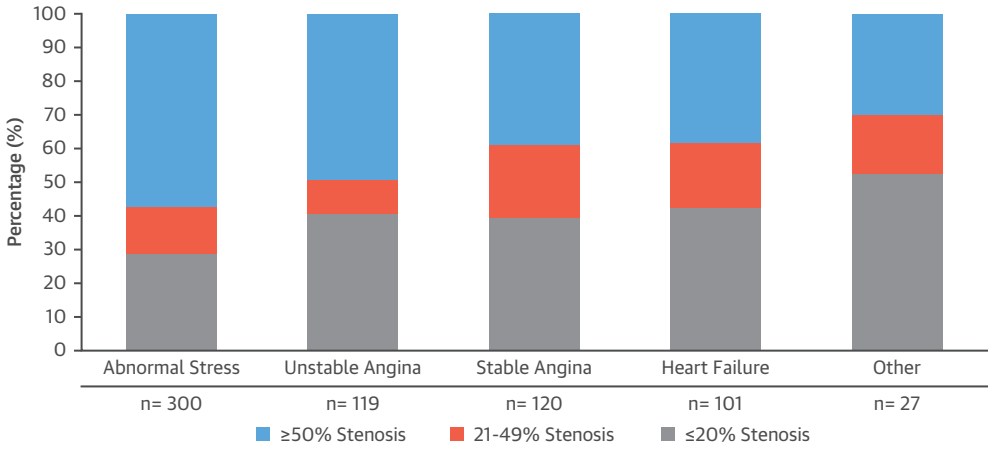
FIGURE 1 Distribution of NCA and Nonobstructive and Obstructive CAD



Distribution of normal coronary arteries (NCA) (≤20% stenosis), nonobstructive coronary artery disease (CAD) (21% to 49% stenosis), and obstructive CAD (≥50% stenosis) for each referral indication.

obstructive CAD may be due to inappropriate referral to ICA, prompting a call for improvements in pre-ICA risk stratification (2). The use of administrative databases in prior studies has precluded collection of detailed and accurate information pertaining to indications for ICA, clinical characteristics, and pre-test risk of individual patients. A rigorous analysis of the appropriateness of these referrals has therefore not been possible (3).

We performed a detailed medical record review to identify the prevalence of obstructive CAD, pre-test risk, and indication appropriateness in patients without acute myocardial infarction referred for nonemergent index ICA at the University of Virginia between January 1, 2012 and December 31, 2013 for suspected CAD. We hypothesized that ICA would be appropriate and pre-test risk high even in patients with NCA and nonobstructive CAD. Key patient demographics, comorbidities, stress tests, and imaging findings were prospectively entered into the electronic medical record and abstracted retrospectively. ICA was performed using standard clinical protocols with quantitative coronary analysis. NCA was defined as the presence of <20% stenosis in all coronary vessels. Nonobstructive and obstructive CAD were defined by ≥1 coronary artery with a 21% to 49% or ≥50% stenosis, respectively.

We identified 667 consecutive patients (mean age 62.2 years; 54.4% were women). Of these, 239 (35.8%) had NCA, 101 (15.2%) had nonobstructive CAD, and 327 (49.0%) had obstructive CAD. As shown in **Figure 1**, there were substantial rates of NCA or nonobstructive CAD irrespective of referral indication: 42.3% in patients with an abnormal stress test; 55.5% in patients with chest pain syndromes without troponin elevation; and 60.8% in those evaluated for heart failure. The population studied was at intermediate to high risk for CAD, with median atherosclerotic cardiovascular disease (ASCVD) risk score of 17.3% (IQR: 7.5%, 32.1%). Pre-test risk was elevated (ASCVD ≥7.5%) in 74.9% of patients. There were no differences by referral indication in median ASCVD risk ($p = 0.83$) or percentage with ASCVD ≥7.5% ($p = 0.43$). Of the 292 who underwent stress imaging, 267 (91.4%) had abnormal imaging (84.5% with evidence of ischemia and 24.5% with infarction). Of those with ischemia, 40.5% had NCA or nonobstructive CAD. Of those referred for chest pain syndromes, 68.6% had moderate to severe angina (Canadian Cardiovascular Society class 3 or 4) and 75.3% had elevated ASCVD risk. Surprisingly, the rate of NCA or nonobstructive disease remained high at 57.8% in those with an elevated ASCVD risk of ≥7.5% and severe angina (Canadian Cardiovascular Society class 4).

All ICA studies were assessed for appropriateness as classified by the 2012 Appropriate Use Criteria for Diagnostic Catheterization (3). ICA was appropriate in 99.0% of the patient population. None of the 7 inappropriate studies had ASCVD risk ≥7.5% and all had NCA or nonobstructive CAD.

In this cohort of patients who underwent nonemergent, index ICA, the 49.0% rate of obstructive CAD was slightly higher than the median rate of

obstructive CAD (45%) in patients undergoing elective ICA in the NCDR (National Cardiovascular Data Registry), comprising data from almost 700 hospitals (2). Contrary to the suggestion that inappropriate studies and low clinical risk are the primary contributors to the rather high prevalence of NCA or nonobstructive CAD, we found that 99.0% of patients undergoing ICA were appropriately referred and 75% had elevated ASCVD risk ≥7.5%. The rate of NCA or nonobstructive CAD was unexpectedly high even in those referred for ICA with ischemia on noninvasive stress imaging or with severe angina and elevated ASCVD risk. Although the 60% rate of obstructive CAD in those referred for positive stress in our cohort was greater than the 41% prevalence in the NCDR database, the rate of NCA or nonobstructive CAD remained substantial (1). Many of these patients without obstructive CAD may have had angina and ischemia from abnormal coronary flow physiology from either microvascular or endothelial dysfunction (4).

In conclusion, this study shows that despite a high prevalence of normal coronary arteries or nonobstructive CAD, the rate of appropriateness of referral for nonemergent coronary angiography was very high at 99%. Further investigation is warranted to identify better methods for pre-ICA prediction of obstructive CAD in patients with high pre-test CAD probability and an appropriate indication for ICA. Imaging advances will likely play a significant role, including noninvasive coronary anatomic evaluation by computed tomography angiography and improved perfusion assessment with positron emission tomography and cardiac magnetic resonance. Future research should also determine the role of microvascular and endothelial dysfunction in patients with abnormal stress tests or chest pain syndromes who are subsequently shown to have NCA or nonobstructive CAD on ICA.

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Proinflammatory State, Diverse Protective Plasma Proteins Including High-Density Lipoprotein Particles, and Outcome

The population-based CANHEART (Cardiovascular Health in Ambulatory Care Research Team) “big data” cohort examining the relationship between high-density lipoprotein cholesterol (HDL-C) and cause-specific mortality rates was of interest in several aspects (1). These investigators found that this relationship was U-shaped rather than linear; lower HDL-C levels were associated with an increased hazard of mortality, but very high HDL-C levels were also associated with an increased hazard of noncardiovascular mortality. Given the similarities in associations with noncardiovascular outcomes, these investigators (1) concluded that the HDL-C level is unlikely to represent a cardiovascular-specific risk factor or a target for intervention.

This study is a confirmation of those published in the past 8 years, and it finally shifts the focus of the HDL hypothesis away from absolute HDL-C concentrations to HDL-C function. Although our findings (2) were not cited in their paper, we documented, in a population-based longitudinal study among Turkish