Overlap of Atherosclerotic Disease

9

Natalie Gwilliam and Ross Milner

Introduction

The importance of identifying overlap disease aids not only in perioperative management but may explain the long-term success or failure of operative interventions. Arterial disease represents a systemic process; thus, isolated interventions may benefit regional symptoms but do not change the overall prognosis for patients. Mitigating these systemic risk factors would logically not only improve perioperative morbidity and mortality but also long-term survival.

Follow-up data from the REACH registry at 3 years demonstrated, similar to the 1-year follow-up, that patients with multivessel disease had nearly double the event rates (MI, vascular death, rehospitalization) compared to those with single disease (40.5 % vs 25.5 %) [1, 2]. Progression from uni- to poly-vascular disease varies based upon the initial location of disease. Not only progression to poly-vascular disease but event rates also vary based upon the primary vascular bed with PAD carrying the worst prognosis for both progression to multivessel disease and event rate [1].

CAD

Coronary artery disease (CAD) manifests as angina and may culminate as a myocardial infarction (MI) or progress to heart failure (HF). It may also be silent. It is estimated that in the USA alone, 620,000 people will have a new coronary attack, another 295,000 will have a recurrent attack, and 150,000 will have a silent event in 2014. Fatalities from these events account for one out of every six deaths in the USA. This is despite a 39.2 % decrease in the number of deaths attributable to CAD from 2000 to 2010 [3].

Peripheral arterial diseases (PADs) of interest in relationship to CAD include lower extremity arterial disease (LEAD), renal artery stenosis (RAS), and carotid artery stenosis (CAS). Data out of the Cleveland Clinic in the 1980s indicated that patients with a primary diagnosis of PAD of any region carried a 21–41 % incidence of concomitant CAD [4]. Three decades later, a Japanese study of patients undergoing non-emergent CAG for suspicion of CAD found a similar incidence with 24 % of patients having one or more additional beds of disease (2 % CAS and RAS; 3 % CAS and PAD; 3.5 % RAS and PAD; 0.8 % CAS, RAS, PAD) [5].

The incidence of lower extremity arterial disease (LEAD) in CAD patients ranges from 10 to 40 %. Some lower estimates come from studies that use intermittent claudication (IC) as a surrogate for LEAD and thus underreport its prevalence [6–8]. Prevalence also depends on the geographical or ethnic population studied. The aforementioned Japanese study found that of patients undergoing CAG, 16 % had concomitant LEAD [5]. In a cross-sectional study of patients presenting to primary care physicians in France, over a quarter (26.6 %) of patients with CAD had undiagnosed LEAD based on ABIs [9]. At the higher end of the spectrum, Dieter et al. reported 40 % prevalence of PAD in patients hospitalized for stable CAD. The fact that a higher percentage of CAD patients ill enough for hospitalization have PAD is consistent with findings that PAD correlates with higher morbidity and mortality for CAD patients [10].

The coexistence of LEAD in CAD patients is associated with worse prognosis. This has been born out in multiple studies including REACH, GRACE, CASS, and PAMISCA [1, 11–14]. LEAD roughly doubles the morbidity and mortality for CAD patients. This is true for both symptomatic and asymptomatic CAD and symptomatic and asymptomatic LEAD and post-intervention [1, 14–17]. Furthermore, the presence of LEAD can predict the severity of CAD. A study of African-Americans undergoing cardiac catheterization

N. Gwilliam, MD
General Surgery, University of Chicago, Chicago, IL, USA

R. Milner, MD (✉)
Vascular Surgery, Center for Aortic Diseases,
University of Chicago, 5841 S. Maryland Ave.,
MC5028, Chicago, IL 60637, USA

R.S. Dieter et al. (eds.), *Critical Limb Ischemia*, DOI 10.1007/978-3-319-31991-9_9

with simultaneous ABIs found that 90 % of patients with ABI < 0.9 had CAD on angiography. Of those patients found to have severe CAD (three vessel or left main), 86 % had LEAD [18]. This study reinforces findings from larger, historical studies such as the Cardiovascular Health Study that demonstrated associations between ABI, MI, CHF, and angina [19].

The association between renal artery stenosis (RAS) and increased prevalence, severity, and mortality of CAD is well established [20–22]. Previous reports of renal artery stenosis (RAS) in patients with known CAD ranged from 22 to 89 % [23, 24]. These figures are significantly higher than recent studies which assess patients undergoing CAG to study prevalence of RAS in CAD. These studies report a range from 9 to 23 % RAS during CAG [5, 25–28]. In an Austrian study evaluating RAS in patients undergoing CAG, there was an overall rate of 10.7 % RAS, with 2.3 % demonstrating bilateral RAS, defined as ≥50 % luminal narrowing [26]. However, this study did not define what percentage of these patients demonstrated significant CAD. Based upon the authors' models, they did find that increasing numbers of stenotic coronary segments correlated with increased RAS frequency [26]. A Japanese study of similar design also found only 9 % prevalence [5] and a Korean study 9.4 % [29]. The Korean study reported only 26 % CAD in the entire cohort but did find CAD to be a statistically significant predictor of RAS with an odds ratio of 5.6 [29]. In a French study using CAG in patients with known CAD, a higher percentage (14.5 %) had significant unilateral disease of whom 3.1 % had bilateral disease [21]. A Polish study reiterated these findings with RAS ≥ 50 % found in 6 % of patients with one-vessel, 11 % with two-vessel, and 13.2 % in three-vessel CAD [30]. These studies also confirmed the correlation between the number of significant coronary lesions and RAS. Clinical interest in this relationship involves medical management of comorbid HTN. Pharmacological management of CHF and HTN must taken into account, primarily the need for an ACE inhibitor or ARB which may worsen renal function in bilateral renal artery stenosis.

Interest in overlap of CAS in known CAD has primarily been focused on perioperative screening and optimization to prevent incidence of stroke [15]. As a result, prevalence data comes from studies assessing CAS at the time of CAG as part of a preoperative workup. Estimates of CAS in patients with CAD range from 7 to 89 %, depending on imaging modalities and definitions of CAS [31]. For CAS defined as ≥70 % stenosis on ultrasound, there was 10.2 % prevalence. Rate of CAS increased with number of diseased coronary vessels: 1.3 % for one, 5.8 % for two, and 19 % for three vessels [31]. This is similar to older data defining stenosis as >75 % with an 8.7 % prevalence of CAS [32]. A Japanese study evaluated a population by ultrasound and angiography. Rates of CAS defined as >50 % on ultrasound by a number of diseased coronary vessels (one, two, three) were 14.5 %, 21.4 %, and 36 %, respectively. When evaluated angiographically with CAS defined as >70 % luminal stenosis, these numbers decreased significantly to 3.4 %, 7.5 %, and 19.4 % [33]. A British study evaluating stress echo (SE) in new onset chest pain found that carotid intima-media thickness (CIMT) as a measure of CAS had better PPV for CAD than clinical stratification, and the addition of CIMT to SE improved the PPV of CAD from 56 to 70 %. Thirty-seven patients demonstrated CAD on CAG, of whom 33 had CAS based on CIMT (89 %) [34]. The disparity in prevalence between this and previous studies reflects different imaging modalities and definitions of CAS. However, as interest and use of CIMT increases, it will be important to understand how it relates to definitions based on percent stenosis and angiography.

LEAD

LEAD affects 3–10 % of the general population with rates rising with age, up to 12–22 % in those greater than 70, and twice as common in diabetics [35–38]. In the USA, rates increase in non-Hispanic blacks and Mexican Americans but are equivalent among non-Hispanic whites, Hispanics, and Asians [36, 39]. These numbers are relatively consistent in studies from multiple European and North American countries including the USA, England, Holland, Germany, and Italy [7, 38, 40–44]. As mentioned, LEAD, particularly symptomatic disease, correlates with two- to eightfold increase in cardiovascular events, including fatalities [1, 11–14]. Annual rate of death from combined CV etiologies (MI, CVA, vascular death) is 5–7 %, with rates corresponding to symptoms, severity, and a number of affected vascular beds [35, 42, 45]. Similar incidence rates were found in the Peripheral Arteriopathy and Cardiovascular Events (PACE) study, in which Brevetti et al. reported after 24 months of follow-up, 25 % of patients had a nonfatal CV event while 15 % of PAD patients died, 8 % from CV disease. PAD was associated with RR 4.03 for all-cause mortality, RR 7.77 for CV mortality, and RR 3.11 nonfatal CV [40].

Identifying those suffering from LEAD and, therefore, those at greater risk for CV complications, is not straightforward. At least two thirds of those with LEAD (ABI ≤ 0.9) are asymptomatic. Studies reporting only symptomatic LEAD represent more severe disease and thus worse outcomes. Early studies, such as the Whitehall study, had to rely on symptoms to diagnose disease and establish correlation between LEAD and mortality [44]. Later studies investigated both symptomatic and asymptomatic disease. In the Rotterdam study, out of 7715 males and females >55, there was a 19.1 % prevalence of PAD but only 6.3 % reported intermittent claudication (IC) [43]. Meijer et al. also found patients with PAD had an increased incidence of LVH, com-

mon carotid IMT, carotid plaques, and larger distal aortic diameter [43]. An Italian cross-sectional study of primary care patients 40–80 years old (4352 pts) demonstrated symptomatic LEAD in 1.6 % (0–6.4 % by sex and decade). Of those with LEAD, 34 % had CVD, 32 % had CAD, 12 % had previous MI, and 5 % had a previous stroke. In comparison, among controls for sex and age, only 11 % had CVD and 9 % CAD [7]. Other studies report higher rates ranging from 40 to 90 % for CAD and CVD and 50 % for CAS [35, 41, 46].

Incidence of RAS among LEAD patients varies by definition (>50 %, >60 %, >70 % stenosis) and means of identification (ultrasonography, arteriography, CT, MRI). Rates range from 9 to 60 % [5, 15, 24, 35, 43, 47–49]. For example, a single study found a 44.9 % overall rate for RS, but 17.3 % had mild disease, 15.7 % severe disease, and 11.8 % bilateral, where the severity of LEAD positively correlated with incidence of RAS [50]. A similar relationship was found in Japanese cohorts by Imori et al. [5]. They found LEAD to be an independent predictor of RAS in a Japanese population with an overall rate of 21 %. In a separate Japanese study, Endo et al. found 22.9 % had RAS >50 % and 11 % had RAS >75 %, demonstrating a positive correlation between RAS ≥ 50 % and critical limb ischemia (CLI) (HR 2.519) [48]. More proximal PAD also carries a higher prevalence of RAS, with 50 % of patients with aortic, bilateral iliac, femoral, and distal vessel disease having RAS [49].

Cerebrovascular disease is present in almost a quarter of patients with PAD. Incidence of CAS >50 % ranges from 25 to 33 %, while significant CAS >70 % ranges from 14 to 25 % [5, 46, 51, 52]. The shared pathophysiology of atherosclerosis explains the close link between PAD and CAS. In fact, an ABI <0.8 has been found to be an independent risk factor for CAS [51]. Furthermore, the presence of PAD is even a stronger predictor of CAS than CAD, AAA, and CBVD symptoms or carotid bruits [46]. As previously discussed, the presence of LEAD in addition to when ABI is used to predict stroke, the specificity is 92 % though sensitivity is low at 16 % with a likelihood ratio of 2.45 (95 % CI, 1.76–3.41) [53]. Adding ABI to the Framingham Risk Score (FRS) is an alternate means for predicting cardiovascular events and improved the overall performance of a risk calculator [54].

RAS

Prevalence of RAS varies by study from 4 to 18.4 % in the general public [55]. The majority will be unilateral with 12 % of cases bilateral in one study of people >65 years [56]. RAS may be due to atherosclerotic disease, fibromuscular dysplasia, or external compression of the vessels. Manifestations include onset and/or acceleration of renal failure, flash pulmonary edema, and difficult-to-control hypertension. Understanding the etiology of RAS, including uni- vs bilaterality, alters treatment and ultimately outcome. When assessing overlap disease in other vascular beds, RAS relates in two ways. First, RAS may share an atherosclerotic etiology. Second, RAS may serve as the etiology of vascular bed disease. The second relationship is proposed to occur through activation of the RAAS pathway, though any of the numerous hormonal or metabolic pathways intimately associated with the kidneys may play a role [57, 58]. As eloquently discussed by Hostetter, the mechanism of action—and directionality—linking renal failure with cardiovascular disease is yet to be fully elucidated, but the renal vascular bed might actually serve as a canary in the coal mine for systemic vascular health [58]. Early recognition of renal demise allows for early intervention and prevention of progressive systemic vascular disease.

HTN is the most readily recognized symptom of RAS. Outside of essential HTN (EH), RAS is the most common cause of high blood pressure. RAS accounts for 12–27.8 % of patients with HTN [59]. Identifying patients with HTN due to RAS is important because mortality is increased by 23 % versus the general population and 7 % versus EH [60]. Related, there is also increased left ventricular hypertrophy (79 % vs 46 %) [15, 61–63]. Up to 54 % of patients with HF (EF <40 %) will have >50 % RAS, including those with preserved renal function [59]. These patients should be managed differently, as use of ACE inhibitors risks AKI [60]. Alternatively, procedure interventions with stenting were initially thought to decrease MAPs and LVH more than medications [64–66]. However, more recent trials such as CORAL found optimal medical therapy to be equivalent to stenting in regard to blood pressure and mortality [67, 68]. What is clear is that appropriate identification and management of RAS-HTN alters outcome for renal and systemic vascular beds [64]. Comparing to the general population, there are 194.5 adverse events per 1000 patient-years related to CHF compared to 56.3 in the general population [69].

CAD has an increased prevalence and severity among those with RAS [64–68, 70]. Rossi et al. found 58 % of patients with RAS >50 % had clinical evidence of CAD [71]. Multiple studies demonstrate a positive correlation between a number of atherosclerotic coronary arteries and RAS, with Safak et al. finding the following: 11.9 % RAS with one vessel, 25.3 % with two vessels, and 42.7 % with three vessels [59, 71–74]. Severity of CAD also correlates with RAS [26, 73]. Even when controlling for risk factors, RAS maintains an independent association with CAD [55]. Almost three fourths of RAS patients have clinical or subclinical symptoms, including angina [55]. With long-term follow-up at 10 years, more than a third of patients will have an AMI [72].

ESRD from RAS has been demonstrated to have even worse outcomes than ESRD from alternate etiologies. Fatica et al. found RAS-ESRD to have significantly higher rates of CAD (51 % vs 23 %), CVD (18 % vs 9 %), occlusive PAD

(44 % vs 14 %), HTN (75 % vs 71 %), CHF (47 % vs 29 %), and MI (21 % vs 9 %) [57]. The argument that these differences are the result of increased incidence of HTN—the most clinically recognizable effect of RAS—is less likely than a shared etiology of vascular disease. As noted above, RAS is an independent predictor of mortality compared to EH.

Up to 72.3 % of RAS will have clinical and subclinical evidence of CVD, including increased prevalence of ICA stenosis and CIMT [55]. This increases to 83 % if there is presence of HTN, compared to 43 % for EH in one Japanese autopsy study [73]. Similar to CAD, severity of RAS correlates with severity of carotid disease [71, 74]. Symptomatic disease is also increased, with 175.5 CVA/TIA events for RAS vs 52.9 in the general population per 1000 patient-years [69]. During long-term follow-up, 5 % of patients with RAS will suffer a stroke which increases to 18 % for RAS-ESRD [57, 72].

PAD in any bed is found in 26–50% of those with RAS [49, 75–78]. One study found up to three fourths of patients with moderate to severe RAS have PAD, defined as ABI <0.95 [79]. Zierler et al. found a similar incidence of disease, with 41 % mild LEAD (ABI <0.95), 38 % moderate LEAD (ABI 0.5–0.95), and 21 % severe LEAD (ABI <0.5) [74]. Of patients with severe RAS (≥60 % bilateral or occluded unilateral), 66 % had moderate to severe LEAD [74]. As discussed earlier, severity of RAS correlates with LEAD severity.

Mesenteric Artery Ischemia

Diagnosis of mesenteric artery disease is clinically challenging. Presence of mesenteric atherosclerosis is rarely clinically detected until two vessels are severely stenosed or even occluded due to the highly collateralized vasculature. One study found that in 18 % of the general population >65, significant stenosis of the celiac artery or SMA is present without symptoms [80]. If symptoms are present, it is typically chronic mesenteric ischemia (CMI) with postprandial abdominal angina. Mesenteric atherosclerosis can present acutely and accounts for 25–30 % of acute mesenteric ischemia cases [81]. As a result, mesenteric disease is important to identify but is typically silent and must be sought out based on comorbidities rather than primary symptoms.

Accurate prevalence estimates in the general population are challenging and range from 6 to 10 % in older autopsy studies, 14–24 % based on arteriography, and 17–18 % on recent ultrasonographic studies [56, 80, 82]. Among patients with known atherosclerotic disease, reports range from 8 to 70 % [80, 83–85]. Of patients undergoing elective surgical intervention for CMI, 85 % are found to have coexistent arterial disease in other beds [86]. The rate for LEAD in this population was 78 % [86]. CAD is present in 33–58 % with CHF in 25 % [86–89]. Atkins et al. found CAS in 13 % of patients undergoing endovascular intervention versus 29 % of open repairs [90].

AAA

Aortic abdominal aneurysms are increasing in incidence globally with the exception of Western Europe, where morbidity and mortality have been decreasing since the 1990s [91, 92]. Prevalence is related to increasing age, male sex, and smoking. For small AAAs, 2.9–4.9 cm in diameter, prevalence ranges from 1.3 to 12.5 % in men and 0–5.2 % in women, with increasing incidence in older cohorts [91]. Risk factors overlap between the two forms of atherosclerosis but biochemical marks and epidemiology are distinct [93]. Though grouped under atherosclerotic disease, the pathophysiology of AAA appears distinct from occlusive atherosclerosis. One group out of Norway found no correlation between size of AAA and atherosclerosis of other beds which may suggest that occlusive atherosclerosis and AAA are parallel rather than sequential processes [94].

Globally, CAD ranges from 25 to 60 % in patients with AAA [4, 95–98]. An Italian study reported the incidence of CAD as 25 % in AAA patients qualifying for surgery (AAA >4.5 cm) [93]. Of patients undergoing surgery for AAA, a study found serious cardiac events associated with 32 % of operations and severe events with 24 % [99]. Within the subgroup of AAA with CAD, 33–43 % will have severe CAD amenable to operative intervention [100, 101].

Additional affected beds include the renal and mesenteric arteries. RAS >50 % occurs in 22–38 % [102]. A more recent report found 23.9 % of patients with AAA had more severe RAS >75 % [103]. In a meta-analysis of AAA and RAS, the pooled prevalence was 33.1 %, demonstrating consistent finding across time and methods [59]. Mesenteric arterial stenosis occurs at a slightly higher rate of 40 % [102]. CAS occurred in 27 % of men with AAA though in a study directly comparing rates of CAS between AAA and CAD patients, CAS in AAA was only 9 % [93, 104].

CAS

CAS accounts for approximately 20 % of ischemic cerebral vascular accidents with a mortality rate of 10–30 % [15]. For those who survive, they face an ever-increasing risk of recurrent cerebral events due to both progressive disease and age. Even asymptomatic patients with >60 % stenosis have a 16 % risk of stroke over 5 years [105]. As is obvious at this point, atherosclerotic disease in one bed correlates with increased rates in other regions resulting in increased morbidity and mortality, particularly cardiac pathologies. For CAS, the concomitant incidence of CAD is from 28 to 32 % [106]. The incidence of LEAD is 43 % and RAS 31 % in a Japanese study [5]. Interestingly, patients with CAS and PAD had higher rates of stokes, MI, and death of cardiovascular etiology than those with CAS and CAD [107]. Nearly a quarter of those with TIA/stroke and symptomatic PAD were hospitalized or had another vascular event within 1 year [107].

References

1. Alberts MJ, et al. Three-year follow-up and event rates in the international REduction of Atherothrombosis for Continued Health Registry. Eur Heart J. 2009;30(19):2318–26. doi:10.1093/eurheartj/ehp355.
2. Steg P, Bhatt DL, Wilson PF, et al. One-year cardiovascular event rates in outpatients with atherothrombosis. JAMA. 2007;297:1197–206.
3. Ripa RS, Kjaer A, Hesse B. Non-invasive imaging for subclinical coronary atherosclerosis in patients with peripheral artery disease. Curr Atheroscler Rep. 2014;16:1–8.
4. Hertzer NR, et al. Coronary artery disease in peripheral vascular patients. A classification of 1000 coronary angiograms and results of surgical management. Ann Surg. 1984;199:223.
5. Imori Y, et al. Co-existence of carotid artery disease, renal artery stenosis, and lower extremity peripheral arterial disease in patients with coronary artery disease. Am J Cardiol. 2014;113:30–5.
6. Criqui MH. Peripheral arterial disease—epidemiological aspects. Vasc Med. 2001;6:3–7.
7. Brevetti G, Oliva G, Silvestro A, Scopacasa F, Chiariello M. Prevalence, risk factors and cardiovascular comorbidity of symptomatic peripheral arterial disease in Italy. Atherosclerosis. 2004;175:131–8.
8. Hirsch AT, Hiatt WR & PARTNERS Steering Committee. PAD awareness, risk, and treatment: new resources for survival—the USA PARTNERS program. Vasc Med. 2001;6:9–12.
9. Kownator S, et al. Prevalence of unknown peripheral arterial disease in patients with coronary artery disease: data in primary care from the IPSILON study. Arch Cardiovasc Dis. 2009;102:625–31.
10. Dieter RS, et al. Lower extremity peripheral arterial disease in hospitalized patients with coronary artery disease. Vasc Med. 2003;8:233–6.
11. Ohman EM, et al. The REduction of Atherothrombosis for Continued Health (REACH) Registry: an international, prospective, observational investigation in subjects at risk for atherothrombotic events-study design. Am Heart J. 2006;151:786–e1.
12. Bertomeu V, et al. Prevalence and prognostic influence of peripheral arterial disease in patients ≥40 years old admitted into hospital following an acute coronary event. Eur J Vasc Endovasc Surg. 2008;36:189–96.
13. Mukherjee D, et al. Impact of prior peripheral arterial disease and stroke on outcomes of acute coronary syndromes and effect of evidence-based therapies (from the Global Registry of Acute Coronary Events). Am J Cardiol. 2007;100:1–6.
14. Eagle KA, Rihal CS, Foster ED, Mickel MC, Gersh BJ. Long-term survival in patients with coronary artery disease: importance of peripheral vascular disease. J Am Coll Cardiol. 1994;23:1091–5.
15. Tendera M, et al. ESC guidelines on the diagnosis and treatment of peripheral artery diseases document covering atherosclerotic disease of extracranial carotid and vertebral, mesenteric, renal, upper and lower extremity arteries: the Task Force on the Diagnosis and Treatment of Peripheral Artery Diseases of the European Society of Cardiology (ESC). Eur Heart J. 2011;32:2851–906.
16. Saw J, et al. The influence of peripheral arterial disease on outcomes: a pooled analysis of mortality in eight large randomized percutaneous coronary intervention trials. J Am Coll Cardiol. 2006;48:1567–72.
17. Parikh SV, et al. Risk of death and myocardial infarction in patients with peripheral arterial disease undergoing percutaneous coronary intervention (from the National Heart, Lung and Blood Institute Dynamic Registry). Am J Cardiol. 2011;107:959–64.
18. Otah KE, et al. Usefulness of an abnormal ankle-brachial index to predict presence of coronary artery disease in African-Americans. Am J Cardiol. 2004;93:481–3.
19. Newman AB, et al. Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. Circulation. 1993;88:837–45.
20. Conlon PJ, Little MA, Pieper K, Mark DB. Severity of renal vascular disease predicts mortality in patients undergoing coronary angiography. Kidney Int. 2001;60:1490–7.
21. Ollivier R, et al. Frequency and predictors of renal artery stenosis in patients with coronary artery disease. Cardiovasc Revasc Med. 2009;10:23–9.
22. Amighi J, et al. Renal artery stenosis predicts adverse cardiovascular and renal outcome in patients with peripheral artery disease. Eur J Clin Invest. 2009;39:784–92.
23. Crowley JJ, et al. Progression of renal artery stenosis in patients undergoing cardiac catheterization. Am Heart J. 1998;136:913–8.
24. Jean WJ, et al. High incidence of renal artery stenosis in patients with coronary artery disease. Cathet Cardiovasc Diagn. 1994;32:8–10.
25. White CJ, et al. Indications for renal arteriography at the time of coronary arteriography: a science advisory from the American Heart Association Committee on Diagnostic and Interventional Cardiac Catheterization, Council on Clinical Cardiology, and the Councils on Cardiovascular Radiology and Intervention and on Kidney in Cardiovascular Disease. Circulation. 2006;114:1892–5.
26. Weber-Mzell D, Kotanko P, Schumacher M, Klein W, Skrabal F. Coronary anatomy predicts presence or absence of renal artery stenosis. A prospective study in patients undergoing cardiac catheterization for suspected coronary artery disease. Eur Heart J. 2002;23:1684–91.
27. Rihal CS, et al. Incidental renal artery stenosis among a prospective cohort of hypertensive patients undergoing coronary angiography. Mayo Clin Proc. 2002;77:309–16.
28. Vetrovec GW, Landwehr DM, Edwards VL. Incidence of renal artery stenosis in hypertensive patients undergoing coronary angiography. J Interv Cardiol. 1989;2:69–76.
29. Lee Y, Shin J-H, Park H-C, Kim SG, Choi S. A prediction model for renal artery stenosis using carotid ultrasonography measurements in patients undergoing coronary angiography. BMC Nephrol. 2014;15:60.
30. Przewlocki T, et al. Prevalence and prediction of renal artery stenosis in patients with coronary and supraaortic artery atherosclerotic disease. Nephrol Dial Transplant. 2008;23:580–5.
31. Kablak-Ziembicka A, et al. Association of increased carotid intima-media thickness with the extent of coronary artery disease. Heart. 2004;90:1286–90.
32. Faggioli GL, Curl GR, Ricotta JJ. The role of carotid screening before coronary artery bypass. J Vasc Surg. 1990;12:724–31.
33. Tanimoto S, et al. Prevalence of carotid artery stenosis in patients with coronary artery disease in Japanese population. Stroke. 2005;36:2094–8.
34. Ahmadvazir S, Zacharias K, Shah BN, Pabla JS, Senior R. Role of simultaneous carotid ultrasound in patients undergoing stress echocardiography for assessment of chest pain with no previous history of coronary artery disease. Am Heart J. 2014;168:229–36.
35. Norgren L, et al. Inter-society consensus for the management of peripheral arterial disease (TASC II). Eur J Vasc Endovasc Surg. 2007;33:S1–75.
36. Gregg EW, et al. Prevalence of lower-extremity disease in the U.S. adult population ≥40 years of age with and without diabetes 1999–2000 national health and nutrition examination survey. Diabetes Care. 2004;27:1591–7.
37. Criqui MH, et al. The prevalence of peripheral arterial disease in a defined population. Circulation. 1985;71:510–5.
38. Diehm C, et al. High prevalence of peripheral arterial disease and co-morbidity in 6880 primary care patients: cross-sectional study. Atherosclerosis. 2004;172:95–105.

39. Criqui MH, et al. Ethnicity and peripheral arterial disease the San Diego population study. Circulation. 2005;112:2703–7.
40. Brevetti G, et al. Peripheral arterial disease and cardiovascular risk in Italy. Results of the Peripheral Arteriopathy and Cardiovascular Events (PACE) study. J Cardiovasc Med. 2006;7:608–13.
41. Van Kuijk J-P, et al. Long-term prognosis of patients with peripheral arterial disease with or without polyvascular atherosclerotic disease. Eur Heart J. 2010;31:992–9.
42. Murabito JM, D'Agostino RB, Silbershatz H, Wilson PWF. Intermittent claudication: a risk profile from the Framingham Heart Study. Circulation. 1997;96:44–9.
43. Meijer WT, et al. Peripheral arterial disease in the elderly: the Rotterdam study. Arterioscler Thromb Vasc Biol. 1998;18:185–92.
44. Smith GD, Shipley MJ, Rose G. Intermittent claudication, heart disease risk factors, and mortality. The Whitehall study. Circulation. 1990;82:1925–31.
45. Criqui MH, et al. Mortality over a period of 10 years in patients with peripheral arterial disease. N Engl J Med. 1992;326:381–6.
46. Golomb BA, Dang TT, Criqui MH. Peripheral arterial disease morbidity and mortality implications. Circulation. 2006;114:688–99.
47. Ozkan U, Oguzkurt L, Tercan F, Nursal TZ. The prevalence and clinical predictors of incidental atherosclerotic renal artery stenosis. Eur J Radiol. 2009;69:550–4.
48. Endo M, et al. Prevalence and risk factors for renal artery stenosis and chronic kidney disease in Japanese patients with peripheral arterial disease. Hypertens Res. 2010;33:911–5.
49. Metcalfe W, Reid AW, Geddes CC. Prevalence of angiographic atherosclerotic renal artery disease and its relationship to the anatomical extent of peripheral vascular atherosclerosis. Nephrol Dial Transplant. 1999;14:105–8.
50. Missouris CG, Buckenham T, Cappuccio FP, MacGregor GA. Renal artery stenosis: a common and important problem in patients with peripheral vascular disease. Am J Med. 1994;96:10–4.
51. Cinà CS, Safar HA, Maggisano R, Bailey R, Clase CM. Prevalence and progression of internal carotid artery stenosis in patients with peripheral arterial occlusive disease. J Vasc Surg. 2002;36:75–82.
52. Ahmed B, Al-Khaffaf H. Prevalence of significant asymptomatic carotid artery disease in patients with peripheral vascular disease: a meta-analysis. Eur J Vasc Endovasc Surg. 2009;37:262–71.
53. Doobay AV, Anand SS. Sensitivity and specificity of the Ankle–Brachial index to predict future cardiovascular outcomes: a systematic review. Arterioscler Thromb Vasc Biol. 2005;25:1463–9.
54. Fowkes FGR, et al. Development and validation of an ankle brachial index risk model for the prediction of cardiovascular events. Eur J Prev Cardiol. 2014;21:310–20.
55. Edwards MS, et al. Associations between renovascular disease and prevalent cardiovascular disease in the elderly: a population-based study. Vasc Endovascular Surg. 2004;38:25–35.
56. Hansen KJ, et al. Prevalence of renovascular disease in the elderly: a population-based study. J Vasc Surg. 2002;36:443–51.
57. Fatica RA, Port FK, Young EW. Incidence trends and mortality in end-stage renal disease attributed to renovascular disease in the United States. Am J Kidney Dis. 2001;37:1184–90.
58. Hostetter TH. Chronic kidney disease predicts cardiovascular disease. N Engl J Med. 2004;351:1344–6.
59. De Mast Q, Beutler JJ. The prevalence of atherosclerotic renal artery stenosis in risk groups: a systematic literature review. J Hypertens. 2009;2009(27):1333–40.
60. Zoccali C, Mallamaci F, Finocchiaro P. Atherosclerotic renal artery stenosis: epidemiology, cardiovascular outcomes, and clinical prediction rules. J Am Soc Nephrol. 2002;13:S179–83.
61. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Left ventricular mass and incidence of coronary heart disease in an elderly cohort. Ann Intern Med. 1989;110:101–7.
62. Levy D, Garrison RJ, Savage DD, Kannel WB, Castelli WP. Prognostic implications of echocardiographically determined left ventricular mass in the Framingham Heart Study. N Engl J Med. 1990;322:1561–6.
63. Wright JR, et al. Left ventricular morphology and function in patients with atherosclerotic renovascular disease. J Am Soc Nephrol. 2005;16:2746–53.
64. Zeller T, et al. Regression of left ventricular hypertrophy following stenting of renal artery stenosis. J Endovasc Ther. 2007;14:189–97.
65. Van Jaarsveld B, et al. The Dutch Renal Artery Stenosis Intervention Cooperative (DRASTIC) Study: rationale, design and inclusion data. J Hypertens Suppl. 1998;16:S21–7.
66. Krijnen P, et al. A clinical prediction rule for renal artery stenosis. Ann Intern Med. 1998;129:705–11.
67. Cooper CJ, et al. Stent revascularization for the prevention of cardiovascular and renal events among patients with renal artery stenosis and systolic hypertension: rationale and design of the CORAL trial. Am Heart J. 2006;152:59–66.
68. Cooper CJ, et al. Stenting and medical therapy for atherosclerotic renal-artery stenosis. N Engl J Med. 2013;370:13–22.
69. Kalra PA, et al. Atherosclerotic renovascular disease in United States patients aged 67 years or older: risk factors, revascularization, and prognosis. Kidney Int. 2005;68:293–301.
70. MacDowall P, et al. Risk of morbidity from renovascular disease in elderly patients with congestive cardiac failure. Lancet. 1998;352:13–6.
71. Rossi G, et al. Excess prevalence of extracranial carotid artery lesions in renovascular hypertension. Am J Hypertens. 1992;5:8–15.
72. Safak E, et al. Long-term follow-up of patients with atherosclerotic renal artery disease. J Am Soc Hypertens. 2013;7:24–31.
73. Uzu T, et al. Prevalence and predictors of renal artery stenosis in patients with myocardial infarction. Am J Kidney Dis. 1997;29:733–8.
74. Zierler R, Bergelin RO, Polissar NL, et al. Carotid and lower extremity arterial disease in patients with renal artery atherosclerosis. Arch Intern Med. 1998;158:761–7.
75. Olin JW, Melia M, Young JR, Graor RA, Risius B. Prevalence of atherosclerotic renal artery stenosis in patients with atherosclerosis elsewhere. Am J Med. 1990;88:46N–51.
76. Harding MB, et al. Renal artery stenosis: prevalence and associated risk factors in patients undergoing routine cardiac catheterization. J Am Soc Nephrol. 1992;2:1608–16.
77. Valentine RJ, et al. The coronary risk of unsuspected renal artery stenosis. J Vasc Surg. 1993;18:433–40.
78. Wilms G, Marchal G, Peene P, Baert AL. The angiographic incidence of renal artery stenosis in the arteriosclerotic population. Eur J Radiol. 1990;10:195–7.
79. Tollefson DFJ, Ernst CB. Natural history of atherosclerotic renal artery stenosis associated with aortic disease. J Vasc Surg. 1991;14:327–31.
80. Wilson DB, et al. Clinical course of mesenteric artery stenosis in elderly Americans. Arch Intern Med. 2006;166:2095–100.
81. Cangemi JR, Picco MF. Intestinal Ischemia in the elderly. Gastroenterol Clin North Am. 2009;38:527–40.
82. Hirsch AT, et al. ACC/AHA 2005 guidelines for the management of patients with peripheral arterial disease (lower extremity, renal, mesenteric, and abdominal aortic): a collaborative report from the American Association for Vascular Surgery/Society for Vascular Surgery, Society for Cardiovascular Angiography and Interventions, Society for Vascular Medicine and Biology, Society of Interventional Radiology, and the ACC/AHA Task Force on Practice Guidelines (Writing Committee to Develop Guidelines for the Management of Patients with Peripheral Arterial Disease). J Am Coll Cardiol. 2006;47:e1–e192.

83. Ghosh S, Roberts N, Firmin RK, Jameson J, Spyt TJ. Risk factors for intestinal ischaemia in cardiac surgical patients. Eur J Cardiothorac Surg. 2002;21:411–6.
84. Mensink PBF, et al. Clinical significance of splanchnic artery stenosis. Br J Surg. 2006;93:1377–82.
85. Taylor Jr LM, Moneta GL. Intestinal ischemia. Ann Vasc Surg. 1991;5:403–6.
86. Mateo RB, et al. Elective surgical treatment of symptomatic chronic mesenteric occlusive disease: early results and late outcomes. J Vasc Surg. 1999;29:821–32.
87. Valentine RJ, Martin JD, Myers SI, Rossi MB, Clagett GP. Asymptomatic celiac and superior mesenteric artery stenoses are more prevalent among patients with unsuspected renal artery stenoses. J Vasc Surg. 1991;14:195–9.
88. Thomas JH, Blake K, Pierce GE, Hermreck AS, Seigel E. The clinical course of asymptomatic mesenteric arterial stenosis. J Vasc Surg. 1998;27:840–4.
89. Peck MA, et al. Intermediate-term outcomes of endovascular treatment for symptomatic chronic mesenteric ischemia. J Vasc Surg. 2010;51:140–147.e2.
90. Atkins MD, et al. Surgical revascularization versus endovascular therapy for chronic mesenteric ischemia: a comparative experience. J Vasc Surg. 2007;45:1162–71.
91. Go AS, et al. Heart disease and stroke statistics—2014 update a report from the American Heart Association. Circulation. 2014;129:e28–292.
92. Li X, Zhao G, Zhang J, Duan Z, Xin S. Prevalence and trends of the abdominal aortic aneurysms epidemic in general population—a meta-analysis. PLoS One. 2013;8.
93. Palazzuoli A, et al. Prevalence of risk factors, coronary and systemic atherosclerosis in abdominal aortic aneurysm: comparison with high cardiovascular risk population. Vasc Health Risk Manag. 2008;4:877–83.
94. Johnsen SH, Forsdahl SH, Singh K, Jacobsen BK. Atherosclerosis in abdominal aortic aneurysms: a causal event or a process running in parallel? The Tromsø study. Arterioscler Thromb Vasc Biol. 2010;30:1263–8.
95. Hollier LH, et al. Late survival after abdominal aortic aneurysm repair: influence of coronary artery disease. J Vasc Surg. 1984;1:290–9.
96. Roger VL, et al. Influence of coronary artery disease on morbidity and mortality after abdominal aortic aneurysmectomy: a population-based study, 1971–1987. J Am Coll Cardiol. 1989;14:1245–52.
97. Johnston KW. Multicenter prospective study of nonruptured abdominal aortic aneurysm. Part II variables predicting morbidity and mortality. J Vasc Surg. 1989;9:437–47.
98. Sakalihasan N, Limet R, Defawe O. Abdominal aortic aneurysm. Lancet. 2005;365:1577–89.
99. Kumar R, et al. Adverse cardiac events after surgery. J Gen Intern Med. 2001;16:507–18.
100. Hertzer NR, Young JR, Kramer JR, et al. Routine coronary angiography prior to elective aortic reconstruction: results of selective myocardial revascularization in patients with peripheral vascular disease. Arch Surg. 1979;114:1336–44.
101. Starr JE, et al. Influence of gender on cardiac risk and survival in patients with infrarenal aortic aneurysms. J Vasc Surg. 1996;23:870–80.
102. Valentine RJ, Myers SI, Miller GL, Lopez MA, Clagett GP. Detection of unsuspected renal artery stenoses in patients with abdominal aortic aneurysms: refined indications for preoperative aortography. Ann Vasc Surg. 1993;7:220–4.
103. Kuroda S, et al. Prevalence of renal artery stenosis in autopsy patients with stroke. Stroke. 2000;31:61–5.
104. Sukhija R, Aronow WS, Yalamanchili K, Sinha N, Babu S. Prevalence of coronary artery disease, lower extremity peripheral arterial disease, and cerebrovascular disease in 110 men with an abdominal aortic aneurysm. Am J Cardiol. 2004;94:1358–9.
105. Inzitari D, et al. The causes and risk of stroke in patients with asymptomatic internal-carotid-artery stenosis. N Engl J Med. 2000;342:1693–701.
106. Hertzer NR, et al. Coronary angiography in 506 patients with extracranial cerebrovascular disease. Arch Intern Med. 1985;145:849–52.
107. Banerjee A, Fowkes FG, Rothwell PM. Associations between peripheral artery disease and ischemic stroke implications for primary and secondary prevention. Stroke. 2010;41:2102–7.