Renal Insufficiency and the Risk of Lower Extremity Peripheral Arterial Disease: Results from the Heart and Estrogen/Progestin Replacement Study (HERS)

ANN M. O'HARE,* ERIC VITTINGHOFF,† JUDITH HSIA,‡ and MICHAEL G. SHLIPAK*†

**Departments of Medicine, VA Medical Center San Francisco and University of California, San Francisco, California; †Department of Epidemiology and Biostatistics, University of California, San Francisco, California; and ‡Department of Medicine, George Washington University, Washington, DC.*

Abstract. Renal insufficiency is a risk factor for coronary heart disease and stroke, but whether it predicts lower extremity peripheral arterial disease (PAD) is unknown. The authors evaluated was the association of baseline renal insufficiency with future PAD events in the Heart and Estrogen/Progestin Replacement Study (HERS) and follow-up study (HERS II). A total of 2763 postmenopausal women with known coronary heart disease were enrolled in HERS and randomly assigned to receive hormone therapy with conjugated estrogens and medroxyprogesterone acetate or placebo and followed for up to 8 yr for clinical end points. The outcome was time from randomization to first occurrence of either a lower extremity amputation, revascularization (surgical or percutaneous), or lumbar sympathectomy during follow-up. Incident lower extremity PAD event rates among women with creatinine clearances ≥60, 30 to 59, and <30 ml/min/1.73 m^2 were, respectively, 0.55%, 0.92%, and 2.73% per year. After multivariable proportional-hazard adjustment for potential confounders and other known risk factors for PAD, women with a creatinine clearance 30 to 59 ml/min/1.73 m^2 (hazard ratio [HR], 1.63; 95% confidence interval [CI], 1.04 to 2.54, $P = 0.032$) and <30 ml/min/1.73 m^2 (HR, 3.24; 95% CI, 1.20 to 8.78, $P = 0.021$) had a significantly increased risk of PAD compared with participants with a creatinine clearance ≥60 ml/min/1.73 m^2. Renal insufficiency was independently associated with future PAD events among postmenopausal women with coronary heart disease. Future studies should determine whether this association is present in other populations and investigate its potential mechanisms.

The prevalence of peripheral arterial disease (PAD) is high among patients with renal insufficiency and end-stage renal disease, and hemodialysis patients experience lower extremity amputation rates that are tenfold greater than among elderly persons with diabetes in the general population (1–5). Many studies have now demonstrated that renal insufficiency is a risk factor for cardiovascular death, coronary heart disease, and stroke (6–10), but most did not examine its association with lower extremity PAD; conversely, epidemiologic studies of PAD have not evaluated renal insufficiency as a potential predictor (11–16). Thus, although renal disease might be expected to have a longitudinal association with PAD, as it has for other forms of cardiovascular disease, an association has not been demonstrated between renal insufficiency and incident PAD events, such as amputation and lower extremity revascularization.

Studies of PAD risk factors have been further limited by the fact that early disease is minimally symptomatic and often escapes clinical attention and documentation (17). Measurable PAD clinical end points are relatively uncommon and are usually limited to severe disease complications (*e.g.*, rest pain, foot ulceration, and gangrene) that require surgical intervention via amputation or revascularization. Because few clinical studies have rigorously measured PAD end points, the identification of unique risk factors for PAD has been challenging.

The Heart and Estrogen/Progestin Replacement Study (HERS) was a unique cohort of postmenopausal women with established coronary artery disease who were randomly assigned to receive hormone therapy with estrogens and progestin or placebo and followed for up to 8 yr for the occurrence of cardiovascular end points (including lower extremity PAD) and death (18). Because all HERS participants had coronary artery disease, we believed that they would also have an increased incidence of PAD events that would permit us to explore the association of renal insufficiency with PAD. We hypothesized that among HERS participants, baseline renal insufficiency would be an independent risk factor for the future development of lower extremity PAD complications.

Received October 28, 2003. Accepted January 14, 2004.

Correspondence to Dr. Ann M. O'Hare, Nephrology Division, Box 111J VA Medical Center San Francisco, 4150 Clement Street, San Francisco, CA 94121. Phone: 415-221-4810 ext. 4953; Fax: 415-750-6949; E-mail: Ann.O'Hare@med.va.gov

1046-6673/1504-1046
Journal of the American Society of Nephrology

DOI: 10.1097/01.ASN.0000119574.27772.FD

Materials and Methods

Study Design

HERS was a randomized double-blinded, placebo-controlled trial of the effect of daily conjugated estrogens plus medroxyprogesterone acetate on coronary heart disease risk among 2763 postmenopausal women with documented coronary heart disease (18). Study participants were enrolled between February 1993 and September 1994, and the trial was completed in 1998. At the end of the study period, participants were informed of their treatment status and instructed to make a decision regarding postmenopausal hormone use in consultation with their personal physician. At this time, all surviving participants were invited to enroll in follow-up (HERS II) (19). A total of 2321 women (93% of those surviving) enrolled in HERS II, which extended follow-up to January 2001. The primary outcome for HERS and HERS II was nonfatal myocardial infarction and death due to coronary heart disease. PAD was a prespecified secondary outcome. Study participants were contacted every 4 mo during follow-up. When potential cardiovascular events were reported, hospital records were requested and independently reviewed by two physicians blinded to treatment arm (for HERS) and to open-label hormone use (for HERS II) at the HERS coordinating center. Event adjudication required reviewer consensus or a third physician to resolve discordant classifications.

Definition of Renal Insufficiency

Estimated creatinine clearance was the main predictor variable for all analyses. We used the Cockroft-Gault formula to estimate creatinine clearance at the time of enrollment in HERS (20). Estimated creatinine clearance was standardized to body surface area by using the formula of Dubois and Dubois (21). We modeled creatinine clearance as a categorical variable whereby women with an estimated creatinine clearance between 30 and 59 ml/min/1.73 m^2 (moderate renal insufficiency) and $<$30 ml/min/1.73 m^2 (severe renal insufficiency) were compared with the reference category of women with an estimated creatinine clearance $\geq$60 ml/min/1.73 m^2 (normal or mildly reduced renal function). We also examined the graded association of creatinine clearance with the outcome within the moderate renal insufficiency category by using cutpoints of 30 to 44 and 45 to 59 ml/min/1.73 m^2. Finally, we also report the association with serum creatinine by using cutpoints corresponding to the 75th and 90th percentiles of creatinine distribution in HERS (1.2 and 1.4 mg/dl, respectively). We selected these cutpoints to be consistent with an earlier analysis of renal insufficiency and cardiovascular outcomes in HERS (10).

Baseline Covariates

At the time of study enrollment, HERS participants underwent baseline physical examination, phlebotomy, and interview in which they were asked about their behavioral risk factors and medical history. For the purposes of this analysis, race was categorized as white, black, or other. Women were considered to have diabetes if they had ever been told they had diabetes or if they had a fasting glucose $>$125 mg/dl at baseline. To adjust for diabetes severity, women were further classified according to whether their diabetes was treated with oral hypoglycemic agents, was treated with oral hypoglycemic agents, insulin, or was untreated. We considered participants to have hypertension if they reported ever being told they had hypertension or if they had a systolic BP $\geq$140 mmHg and/or a diastolic BP $\geq$90 mmHg at the baseline examination. HDL, triglycerides, and lipoprotein(a) were obtained on a fasting blood sample. LDL was estimated via the Friedewald equation. Body mass index, current smoking, aspirin, and HMG-CoA reductase inhibitor use were ascertained at baseline. We also included HERS treatment group assignment (conjugated estrogens plus medroxyprogesterone acetate *versus* placebo). Alcohol use at the time of study enrollment was dichotomized as any alcohol in the last 30 d *versus* none; educational level was dichotomized as high school graduate *versus* non–high school graduate; and participants were considered to exercise if they reported participating in a regular exercise program or walked at least occasionally for more than 10 min at a time. Information on the number of prior myocardial infarctions and history of coronary artery bypass graft and percutaneous transluminal angioplasty (PTCA) was ascertained by questionnaire and validated by detailed medical record review.

Outcome

The outcome for the present analysis was time from randomization to first lower extremity PAD outcome. Such outcomes included lower extremity bypass with distal anastomosis below the level of the iliac arteries (n = 54), lower extremity angioplasty, endarterectomy, repair/reconstruction, or thrombectomy at the level of the distal aorta or below (n = 58), lower extremity amputation (including toe) in the absence of bypass or angioplasty (n = 13), and lumbar sympathectomy (n = 2).

Statistical Analyses

In descriptive analyses, we compared each renal insufficiency group to the referent category with an estimated clearance $\geq$60 ml/min/1.73 m^2 by either a χ^2 test (for categorical variables), a t test (for normally distributed numeric variables) or a Mann-Whitney U test (for nonnormally distributed numeric variables). We used Cox's proportional-hazard analysis to measure the univariate and multivariate associations of renal insufficiency with time from randomization to first hospitalization for a PAD event. Women were censored at the time of death or most recent follow-up through January 1, 2001. In multivariable analysis, we adjusted for age, race, and cardiovascular risk factors, including diabetes (categorized as untreated, treated with oral agents, or treated with insulin), hypertension, fasting LDL, HDL, triglycerides, lipoprotein(a), current smoking, body mass index alcohol use, and exercise. We also adjusted for aspirin use, HMG-CoA reductase inhibitor use, treatment arm, education, and baseline severity of coronary artery disease (number of prior myocardial infarctions and prior coronary artery bypass graft or PTCA). Body mass index and lipoprotein(a) were nonlinearly associated with the outcome and were thus modeled as linear splines to accommodate the observed nonlinearity. For all variables included in the final model, we tested for interactions with renal function category. The proportional-hazard assumption was tested by standard residual-based techniques.

Results

The study sample consisted of 2757 of the 2763 women enrolled in HERS (six women were excluded because we lacked complete data required for calculation of standardized creatinine clearance). Among these, almost half had an estimated creatinine clearance $<$60 ml/min/1.73 m^2; 1438 women had clearance between 30 and 59; and 44 women had a clearance $<$30 ml/min/1.73 m^2. Table 1 summarizes baseline characteristics across levels of renal function.

Overall, 127 lower extremity PAD events occurred during the follow up period, 44 among women with a clearance $\geq$60 ml/min/1.73 m^2, 78 among women with a clearance between

Table 1. Baseline characteristics by level of estimated creatinine clearance among women enrolled in HERS[a]

	Creatinine clearance (ml/min per 1.73 m^2)		
	≥60 (n = 1275)	30–59 (n = 1438)	<30 (n = 44)
Age ± SD (yr)	63 ± 6	70 ± 6[d]	71 ± 5[d]
Race			
white (%)	88	90	73[c]
black (%)	8	8	25[d]
other (%)	4	3[c]	2
Untreated diabetes	9	7[b]	8
Treated with oral agent	10	8[c]	23*
Treated with insulin	9	9	16
Hypertension (%)	67	70[b]	93[d]
Mean LDL cholesterol ± SD (mg/dl)	147 ± 40	143 ± 36[c]	149 ± 46
Mean HDL cholesterol ± SD (mg/dl)	49 ± 12	51 ± 14[d]	51 ± 17
Median lipoprotein(a) level (25^{th}–75^{th} percentile range)	24 (7 to 53)	27 (7 to 56)	26 (8 to 60)
Mean triglyceride level ± SD (mmHg)	168 ± 63	164 ± 63[b]	190 ± 72[b]
Mean body mass index ± SD (kg/m^2)	31 ± 6	27 ± 5[d]	28 ± 5[d]
Current smoker (%)	16	11[d]	21
Aspirin use at baseline (%)	80	78	57[d]
HMG-CoA reductase inhibitor use at baseline (%)	36	37	41
Estrogen progestin treatment group (%)	51	49	48
Any alcohol use in last 30 d (%)	42	39	32
Exercise	64	65	30[d]
Average number of prior MI	0.6	0.6	0.8[b]
Percent prior CABG	38	44[c]	52
Percent prior PTCA	46	41[b]	34

[a] MI, myocardial infarction; CABG, coronary artery bypass graft; PTCA, percutaneous transluminal angioplasty.
[b] $P \leq 0.05$.
[c] $P \leq 0.01$.
[d] $P \leq 0.001$.

30 and 59 ml/min/1.73 m^2, and 5 among women with a creatinine clearance <30 ml/min/1.73 m^2. Figure 1 shows rates of incident PAD events for incremental categories of creatinine clearance, with results reported for the intermediate categories of 30 to 44 and 45 to 59 ml/min/1.73 m^2. In unadjusted proportional-hazard analysis, creatinine clearance of 30 to 59 and <30 ml/min/1.73 m^2 were associated, respectively, with a 1.6- and almost 5-fold risk for PAD events during follow-up compared with the reference category (Table 2).

The magnitude of the association was not greatly altered by adjustment for other established cardiovascular risk factors, potential confounders, and baseline severity of coronary artery disease. Additionally, there was also a graded increase in risk among those with moderate renal insufficiency: women with a clearance between 30 to 44 ml/min/1.73 m^2 (hazard ratio [HR], 1.85; 95% confidence interval [CI], 1.02 to 3.37, $P = 0.04$) had a higher risk of PAD than women with a clearance of 45 to 60 ml/min/1.73 m^2 (HR, 1.57; 95% CI, 1.00 to 2.48; $P = 0.06$). When creatinine cutpoints were used, relative to women with a serum creatinine <1.2 mg/dl, the adjusted risk of PAD was similar for those with a serum creatinine between 1.2 and 1.4 mg/dl (HR, 1.00; 95% CI, 0.63 to 1.60; $P = 0.96$) but increased for those with a serum creatinine >1.4 mg/dl (HR, 2.28; 95% CI, 1.34 to 3.89; $P = 0.002$).

We detected no statistically significant interactions ($P < 0.05$) between any of the variables included in the multivariable model and renal insufficiency. Specifically, renal insufficiency was associated with PAD even among those without diabetes (HR 1.91 for a clearance 30 to 60 ml/min/1.73 m^2, 95% CI, 1.04 to 3.48; $P = 0.04$ and HR 1.51 for a clearance <30 ml/min/1.73 m^2, 95% CI, 0.18 to 12.40). The proportional-hazard assumption was not violated in any of the above models ($P = 0.99$ for the primary analysis).

Discussion

We herein report strong associations of even moderate renal insufficiency with incident lower extremity PAD events in the HERS and HERS II studies. Compared with women with clearance ≥60 ml/min/1.73 m^2, the risk of reaching a PAD end point was increased by 60% for women with clearance between 30 and 59 ml/min/1.73 m^2 and more than threefold for women with clearance <30 ml/min/1.73 m^2. These associations per-

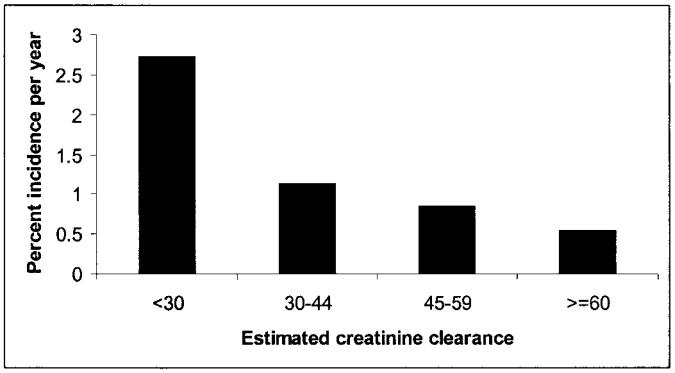

Figure 1. Incident peripheral arterial disease (PAD) events (percentage per year) by level of creatinine clearance for participants in the Heart and Estrogen/Progestin Replacement Study (HERS).

sisted after adjustment for demographic characteristics, other cardiovascular risk factors, potential confounders, and baseline severity of coronary heart disease, as indicated by the number of prior myocardial infarctions and history of coronary artery bypass surgery or PTCA.

In previous studies, risk factors for PAD have included male gender, older age, diabetes, smoking, hypertension, hyperlipidemia, lipoprotein(a), hyperhomocysteinemia, and chronic inflammation, whereas alcohol intake and physical activity appear to be protective (11–16,22–30). However, renal insufficiency—a risk factor for many other forms of cardiovascular disease—had not been considered as a risk factor for lower extremity PAD. This is in part because most previous studies examining the association of renal insufficiency with future cardiovascular events have either not included lower extremity PAD as an outcome or have only included lower extremity PAD events in a composite cardiovascular death or event outcome (7–10). Strikingly, the adjusted association of creatinine clearance <30 ml/min/1.73 m^2 with PAD was similar in magnitude to previously reported associations of established PAD risk factors such as diabetes and current smoking (30).

The finding that persons with moderate renal insufficiency are at increased risk for PAD complications is consistent both with previous studies documenting a high prevalence of PAD and high incidence of lower extremity amputation among patients with end-stage renal disease and with a prior report linking chronic renal insufficiency with the development of claudication (1,2,6). High complication rates after both lower extremity amputation and revascularization in patients with even moderate renal insufficiency further underscore the substantial clinical significance of lower extremity PAD in this population (1,31,32). However, lower extremity PAD has unfortunately received little attention from the nephrology community, with surprisingly few reports evaluating the risk of PAD events or evaluating targeted interventions to prevent PAD complications in this high-risk population (33–35).

In the general population, interventions such as exercise and statin therapy appear to improve the functional limitation associated with lower extremity PAD, and regular foot care and patient and provider education can be extremely effective in preventing amputations among persons with diabetes (36–39). Our findings support concerted efforts to develop, test, and implement strategies to prevent lower extremity PAD complications in persons with renal insufficiency, particularly among those at highest risk for these complications. The increased incidence of PAD complications among persons with renal insufficiency also reinforces the importance of increasing PAD awareness among nephrologists and others caring for these patients

Because the kidney is a highly vascular organ, one possible explanation for the association of renal insufficiency with PAD reported here is that renal disease may merely be a marker for more generalized atherosclerosis. However, the present analysis demonstrates a strong association between renal insufficiency and PAD in a cohort of women with known coronary atherosclerosis despite adjustment for the severity of baseline coronary artery disease (number of prior myocardial infarctions and history of coronary artery bypass graft or PTCA). Potential pathophysiological mechanisms by which decreased GFR might directly predispose to PAD include altered homocysteine metabolism, anemia, oxidative stress, and alterations in inflammatory pathways (40,41). Our findings highlight the need for research to identify possible mechanisms for the association of renal insufficiency with the development of PAD. Investigation along these lines may lead to interventions that would slow disease progression and/or prevent disease complications in this group.

Our study does have certain limitations. First, we were unable to adjust for baseline severity or prevalence of PAD among study participants because information on PAD history was not collected and the ankle-brachial index was not measured in HERS. Because the prevalence of PAD in patients with chronic renal insufficiency is high, further studies are needed to determine whether the association documented here between renal insufficiency and PAD reflects a higher prevalence and greater severity of PAD at baseline among those with renal insufficiency or whether renal insufficiency is in fact a true risk factor for PAD. Second, confounding by severity of other comorbidities included in the model is also a concern. In particular, objective measurements of baseline severity of coronary artery disease such as exercise tolerance testing were not obtained, and data on diabetes severity were limited to serum glucose measurements and method of treatment (*i.e.*, nontreatment, oral agent, or insulin). Third, whereas the surgical end points for lower extremity PAD used in HERS and HERS II are specific and relevant to patient care, use of surgical end points may capture only a subset of persons affected by PAD. For example, a surgical bias against women with renal insufficiency could have affected our results, particularly in the case of elective revascularization procedures performed for noncritical ischemia. However, this should have biased our results toward the null hypothesis. In addition, use of a severe end point such as amputation or revascularization rather than other measures of disease progression, such as the development of intermittent claudication or change in the ankle-brachial index, does not allow us to extrapolate our findings to milder forms of

Table 2. Association of estimated creatinine clearance with development of a lower extremity PAD event[a]

	Creatinine clearance in ml/min per 1.73 m^2		
	≥60(n = 1275)	30–59 (n = 1438)	<30(n = 44)
Total number of events	44	78	5
Event rate per 100 person years (95% confidence interval)	0.55 (0.40 to 0.73)	0.92 (0.73 to 1.15)	2.73 (0.69 to 6.38)
Univariate HR (CI)	1.00 (referent)	1.67 (1.16 to 2.42)	4.95 (1.96 to 12.52)[b]
Multivariate HR (CI)	1.00 (referent)	1.63 (1.04 to 2.54)[d]	3.24 (1.20 to 8.78)[d]

[a] Multivariable analysis is adjusted for age, race, conventional cardiovascular risk factors (diabetes (categorized as treated and untreated) hypertension, fasting LDL, HDL, triglycerides, lipoprotein(a), current smoking, body mass index, alcohol use and exercise) and also aspirin use, HMG-CoA reductase inhibitor use, treatment arm, education, and baseline severity of coronary artery disease (number of prior MI and prior coronary artery bypass graft or PTCA.
[b] $P \leq 0.001$.
[c] $P \leq 0.01$.
[d] $P \leq 0.05$.

PAD. Finally, although we would hypothesize that renal insufficiency is also associated with PAD in men and in those without known coronary artery disease, because of the HERS study design, the present analysis only supports an association in women with established coronary artery disease.

Conclusion

Our findings indicate that even persons with moderate renal insufficiency are at increased risk for future PAD events. Further studies are needed to determine whether this reflects a higher prevalence and/or greater severity of PAD at baseline in those with renal insufficiency or a true independent association between renal insufficiency and development and progression of PAD. Taken together with previous reports of the high prevalence of PAD and high morbidity and mortality associated with both amputation and lower extremity revascularization in patients with renal insufficiency, our results indicate the need for a stronger focus on the prevention and treatment of this disease in persons with even moderate renal insufficiency.

Acknowledgments

HERS and HERS II were supported by Wyeth-Ayerst Laboratories. Drs. O'Hare and Shlipak are supported by Career Development Awards from the Department of Veterans Affairs Health Services Research and Development Program.

References

1. Eggers PW, Gohdes D, Pugh J: Nontraumatic lower extremity amputations in the Medicare end-stage renal disease population. *Kidney Int* 56: 1524–1533, 1999
2. O'Hare A, Johansen K: Lower-extremity peripheral arterial disease among patients with end-stage renal disease. *J Am Soc Nephrol* 12: 2838–2847, 2001
3. Lamar W, V, Casper M, Greenlund K, Zheng ZJ, Giles W, Rith-Najarian S: Prevalence of lower extremity arterial disease defined by the ankle-brachial index among American Indians: The Inter-Tribal Heart Project. *Ethn Dis* 12: S1–S7, 2002
4. Leskinen Y, Salenius JP, Lehtimaki T, Huhtala H, Saha H: The prevalence of peripheral arterial disease and medial arterial calcification in patients with chronic renal failure: Requirements for diagnostics. *Am J Kidney Dis* 40: 472–479, 2002
5. Newman AB, Siscovick DS, Manolio TA, Polak J, Fried LP, Borhani NO, Wolfson SK: Ankle-arm index as a marker of atherosclerosis in the Cardiovascular Health Study. Cardiovascular Heart Study (CHS) Collaborative Research Group. *Circulation* 88: 837–845, 1993
6. Fried LF, Shlipak MG, Crump C, Bleyer AJ, Gottdiener JS, Kronmal RA, Kuller LH, Newman AB: Renal insufficiency as a predictor of cardiovascular outcomes and mortality in elderly individuals. *J Am Coll Cardiol* 41: 1364–1372, 2003
7. Garg AX, Clark WF, Haynes RB, House AA: Moderate renal insufficiency and the risk of cardiovascular mortality: Results from the NHANES I. *Kidney Int* 61: 1486–1494, 2002
8. Manjunath G, Tighiouart H, Coresh J, Macleod B, Salem DN, Griffith JL, Levey AS, Sarnak MJ: Level of kidney function as a risk factor for cardiovascular outcomes in the elderly. *Kidney Int* 63: 1121–1129, 2003
9. Muntner P, He J, Hamm L, Loria C, Whelton PK: Renal insufficiency and subsequent death resulting from cardiovascular disease in the United States. *J Am Soc Nephrol* 13: 745–753, 2002
10. Shlipak MG, Simon JA, Grady D, Lin F, Wenger NK, Furberg CD: Renal insufficiency and cardiovascular events in postmenopausal women with coronary heart disease. *J Am Coll Cardiol* 38: 705–711, 2001
11. Belch JJ, Topol EJ, Agnelli G, Bertrand M, Califf RM, Clement DL, Creager MA, Easton JD, Gavin JR III, Greenland P, Hankey G, Hanrath P, Hirsch AT, Meyer J, Smith SC, Sullivan F, Weber MA: Critical issues in peripheral arterial disease detection and management: A call to action. *Arch Intern Med* 163: 884–892, 2003
12. Criqui MH, Langer RD, Fronek A, Feigelson HS, Klauber MR, McCann TJ, Browner D: Mortality over a period of 10 years in patients with peripheral arterial disease. *N Engl J Med* 326: 381–386, 1992
13. Fowkes FG, Housley E, Cawood EH, Macintyre CC, Ruckley CV, Prescott RJ: Edinburgh Artery Study: Prevalence of asymptomatic and symptomatic peripheral arterial disease in the general population. *Int J Epidemiol* 20: 384–392, 1991

14. Murabito JM, D'Agostino RB, Silbershatz H, Wilson WF: Intermittent claudication: A risk profile from the Framingham Heart Study. *Circulation* 96: 44–49, 1997
15. Murabito JM, Evans JC, Nieto K, Larson MG, Levy D, Wilson PW: Prevalence and clinical correlates of peripheral arterial disease in the Framingham Offspring Study. *Am Heart J* 143: 961–965, 2002
16. Ridker PM, Stampfer MJ, Rifai N: Novel risk factors for systemic atherosclerosis: A comparison of C-reactive protein, fibrinogen, homocysteine, lipoprotein(a), and standard cholesterol screening as predictors of peripheral arterial disease. *JAMA* 285: 2481–2485, 2001
17. Hirsch AT, Criqui MH, Treat-Jacobson D, Regensteiner JG, Creager MA, Olin JW, Krook SH, Hunninghake DB, Comerota AJ, Walsh ME, McDermott MM, Hiatt WR: Peripheral arterial disease detection, awareness, and treatment in primary care. *JAMA* 286: 1317–1324, 2001
18. Grady D, Applegate W, Bush T, Furberg C, Riggs B, Hulley SB: Heart and Estrogen/progestin Replacement Study (HERS): Design, methods, and baseline characteristics. *Control Clin Trials* 19: 314–335, 1998
19. Grady D, Herrington D, Bittner V, Blumenthal R, Davidson M, Hlatky M, Hsia J, Hulley S, Herd A, Khan S, Newby LK, Waters D, Vittinghoff E, Wenger N: Cardiovascular disease outcomes during 6.8 years of hormone therapy: Heart and Estrogen/Progestin Replacement Study follow-up (HERS II). *JAMA* 288: 49–57, 2002
20. Cockroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron* 16: 31–41, 1976
21. Dubois D, Dubois EF: A formula to estimate the approximate surface area if height and weight be known. *Archives of Internal Medicine* 17: 863–871, 1916
22. Fowkes FG, Housley E, Riemersma RA, Macintyre CC, Cawood EH, Prescott RJ, Ruckley CV: Smoking, lipids, glucose intolerance, and blood pressure as risk factors for peripheral atherosclerosis compared with ischemic heart disease in the Edinburgh Artery Study. *Am J Epidemiol* 135: 331–340, 1992
23. Lowe GD, Fowkes FG, Dawes J, Donnan PT, Lennie SE, Housley E: Blood viscosity, fibrinogen, and activation of coagulation and leukocytes in peripheral arterial disease and the normal population in the Edinburgh Artery Study. *Circulation* 87: 1915–1920, 1993
24. MacGregor AS, Price JF, Hau CM, Lee AJ, Carson MN, Fowkes FG: Role of systolic blood pressure and plasma triglycerides in diabetic peripheral arterial disease. The Edinburgh Artery Study. *Diabetes Care* 22: 453–458, 1999
25. Price JF, Mowbray PI, Lee AJ, Rumley A, Lowe GD, Fowkes FG: Relationship between smoking and cardiovascular risk factors in the development of peripheral arterial disease and coronary artery disease: Edinburgh Artery Study. *Eur Heart J* 20: 344–353, 1999
26. Price JF, Lee AJ, Rumley A, Lowe GD, Fowkes FG: Lipoprotein (a) and development of intermittent claudication and major cardiovascular events in men and women: The Edinburgh Artery Study. *Atherosclerosis* 157: 241–249, 2001
27. Smith FB, Lee AJ, Hau CM, Rumley A, Lowe GD, Fowkes FG: Plasma fibrinogen, haemostatic factors and prediction of peripheral arterial disease in the Edinburgh Artery Study. *Blood Coagul Fibrinolysis* 11: 43–50, 2000
28. Housley E, Leng GC, Donnan PT, Fowkes FG: Physical activity and risk of peripheral arterial disease in the general population: Edinburgh Artery Study. *J Epidemiol Community Health* 47: 475–480, 1993
29. Jepson RG, Fowkes FG, Donnan PT, Housley E: Alcohol intake as a risk factor for peripheral arterial disease in the general population in the Edinburgh Artery Study. *Eur J Epidemiol* 11: 9–14, 1995
30. Hsia J, Simon JA, Lin F, Applegate WB, Vogt MT, Hunninghake D, Carr M: Peripheral arterial disease in randomized trial of estrogen with progestin in women with coronary heart disease: The Heart and Estrogen/Progestin Replacement Study. *Circulation* 102: 2228–2232, 2000
31. O'Hare AM, Feinglass J, Reiber GE, Rodriguez RA, Khuri S, Daley J, Henderson WG, and Johansen KL. Post-operative mortality after non-traumatic lower extremity amputation in patients with renal insufficiency. *J Am Soc Nephrol* 15: 427–434, 2004
32. O'Hare AM, Feinglass J, Sidawy AN, Bacchetti P, Rodriguez RA, Daley J, Khuri S, Henderson WG, Johansen KL: Impact of renal insufficiency on short-term morbidity and mortality after lower extremity revascularization: Data from the Department of Veterans Affairs' National Surgical Quality Improvement Program. *J Am Soc Nephrol* 14: 1287–1295, 2003
33. Foster AV, Snowden S, Grenfell A, Watkins PJ, Edmonds ME: Reduction of gangrene and amputations in diabetic renal transplant patients: The role of a special foot clinic. *Diabet Med* 12: 632–635, 1995
34. McMurray SD, Johnson G, Davis S, McDougall K: Diabetes education and care management significantly improve patient outcomes in the dialysis unit. *Am J Kidney Dis* 40: 566–575, 2002
35. Richbourg MJ: Preventing amputations in patients with end stage renal disease: Whatever happened to foot care? *ANNA J* 25: 13–20, 1998
36. Litzelman DK, Slemenda CW, Langefeld CD, Hays LM, Welch MA, Bild DE, Ford ES, Vinicor F: Reduction of lower extremity clinical abnormalities in patients with non–insulin-dependent diabetes mellitus: A randomized, controlled trial. *Ann Intern Med* 119: 36–41, 1993
37. Malone JM, Snyder M, Anderson G, Bernhard VM, Holloway GA Jr, Bunt TJ: Prevention of amputation by diabetic education. *Am J Surg* 158: 520–523, 1989
38. McDermott MM, Guralnik JM, Greenland P, Pearce WH, Criqui MH, Liu K, Taylor L, Chan C, Sharma L, Schneider JR, Ridker PM, Green D, Quann M: Statin use and leg functioning in patients with and without lower-extremity peripheral arterial disease. *Circulation* 107: 757–761, 2003
39. Stewart KJ, Hiatt WR, Regensteiner JG, Hirsch AT: Exercise training for claudication. *N Engl J Med* 347: 1941–1951, 2002
40. Reddan DN, Klassen PS: Chronic kidney disease and cardiovascular risk: Time to focus on therapy. *J Am Soc Nephrol* 13: 2415–2416, 2002
41. Shlipak MG, Fried LF, Crump C, Bleyer AJ, Manolio TA, Tracy RP, Furberg CD, Psaty BM: Elevations of inflammatory and procoagulant biomarkers in elderly persons with renal insufficiency. *Circulation* 107: 87–92, 2003