Cardiovascular risk management in old age

Ruijter, W. de

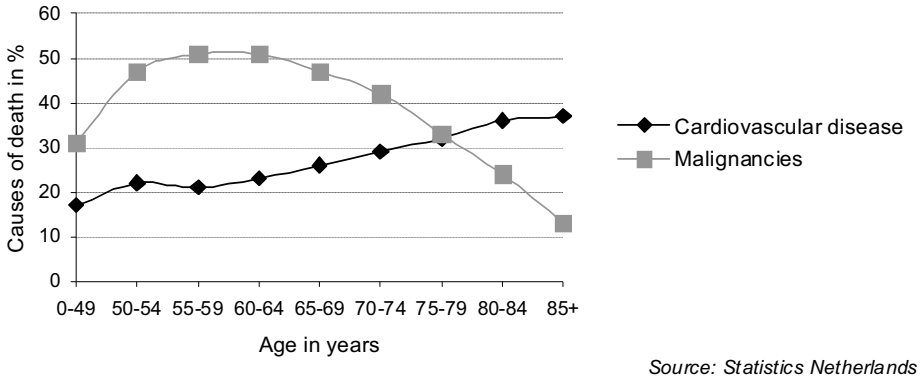
1

General introduction and aims of this thesis

General introduction and aims of this thesis

1.1 The epidemiology and impact of cardiovascular disease in old age

In the Netherlands, as in other industrialized societies, cardiovascular disease is a leading cause of death, accounting for one third of all deaths.[1-4] From all cardiovascular deaths, the majority is caused by ischemic heart disease (29%) and strokes (23%) alone, with heart failure adding another 14%. Mortality from cardiovascular causes, however, is age-dependent: it rises from 17% in people aged <50 years to 37% in the oldest old (≥85 years). In contrast, mortality caused by malignancies reaches its peak in age group 55-64 years (51%), and decreases to a low 13% in the oldest old (Figure 1).[1]



Source: Statistics Netherlands

Figure 1. Causes of death (percentage) by age group in the Netherlands (2006).

When looking at absolute numbers of death, the magnitude of these age differences is more easily imagined. In 2006 cardiovascular disease was responsible for more than 15000 deaths in people aged 85 years and over (62 per 1000 persons of that age), whereas malignancies were accountable for approximately 5500 deaths (22 per 1000 persons of that age) (Figure 2).

Many consider death from cardiovascular disease a relatively 'quick and painless' way to go, and prefer such death to death from malignancies. In fact, case fatality rates of acute cardiovascular events, such as myocardial infarctions, have declined over the last three decades, partly reflecting improvements in treatment of these acute conditions.[5] The increasing number of survivors of *acute* events, however, often develop debilitating *chronic* morbidities such as heart failure and severe neurological deficits, generating huge loss of functional status and quality of life, for both patient and close relatives. Unsurprisingly, with advancing age, cardiovascular disease increasingly dominates assessments of 'burden of disease'.[6]

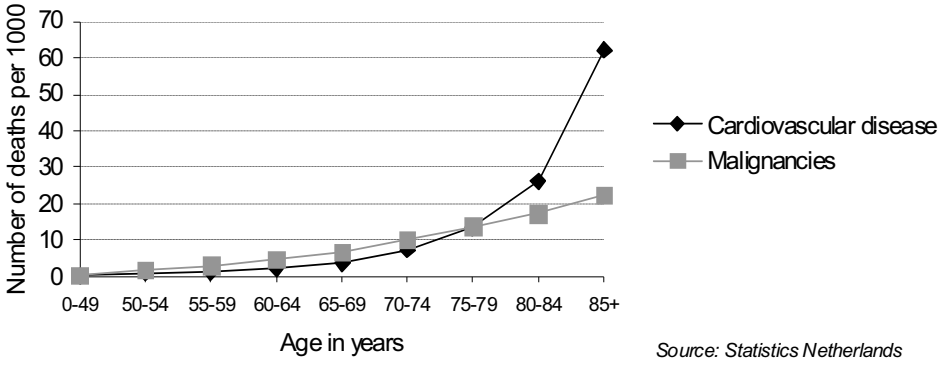


Figure 2. Causes of death (absolute numbers) by age group in the Netherlands (2006).

Obviously, in aging populations the consequences of a rising impact of cardiovascular disease with age are also more serious. In the next three decades, the proportion of people over 65 years of age in the Netherlands will rise from 14 to 24% of the population, and, within this age group, the contribution of those over 80 years of age will almost triple.[7] These joint observations will amplify the over-all impact of cardiovascular disease in older patients in the years to come, and call for appropriate reactions from scientists, clinicians, policy makers and public health forces alike.[8]

An important realisation is that the 'cure and care' for older patients with cardiovascular disease for the greater part is, and probably will remain, a responsibility for primary healthcare workers. These primary healthcare workers will therefore also play a key role in the management of the upcoming wave of cardiovascular disease in old age, across the full spectrum from primary prevention on the one end, up to intensive homecare for end-stage heart failure patients on the other end.[2]

In conclusion, cardiovascular disease comes with age and has a great impact not only on individual patients and their surroundings, but also on (primary) health care professionals and the society as a whole.

1.2 Prevention of cardiovascular disease in old age

As the impact of cardiovascular disease in old age is high, and its prevalence will continue to rise in the decades to come, an important question is whether prevention is possible.

1.2a Secondary prevention

Secondary prevention of cardiovascular disease, obviously, is prevention in high-risk individuals, simply because these patients have a history of

cardiovascular disease, which is a strong risk factor for recurrent cardiovascular events.[2;9;10] Evidence-based treatment of their cardiovascular morbidities includes secondary preventive measures. Despite the growing body of evidence supporting secondary prevention of cardiovascular disease in old age,[11-18] it has been suggested that these preventive measures are not equally offered to older patients.[19-22] In terms of absolute numbers of prevented cardiovascular events, this is a missed opportunity, since even small reductions of relative risk will result in large numbers of absolute prevented events, given the high prevalence of cardiovascular disease in this age group. Since older patients in due course are often cared for by general practitioners, as follow-up after hospital-based and specialist care, it would be valuable to get better insight in general practitioners' current activities and beliefs on this topic, for their role in sustained secondary prevention is pivotal.[2;23;24] Also, adequate secondary prevention of cardiovascular disease in older patients may be improved when easy diagnostic procedures, feasible in primary care, become available, thereby facilitating a better identification of previously unknown cardiovascular disease in older patients.

1.2b Primary prevention

With regard to primary prevention of cardiovascular disease in old age, the prevention-paradox, first described by sir Geoffrey Rose in 1981, should be kept in mind. 'From an epidemiological perspective, it is more efficient to aim preventive measures at populations with mild or moderate increased risks, since the absolute majority of new cases of cardiovascular disease originates from these heterogeneous populations.'[25] On the other hand, case finding by identification of high-risk individuals and subsequent appropriate interventions may result in firm reductions of risk in those individuals, but will not lead to a drastic reduction of cardiovascular disease on a population scale. In all age groups, physicians in daily practice commonly adopt the case finding strategy, while primary preventive measures aimed at populations at large, such as promoting physical exercise, non-smoking and health food, are usually left to the public health sector. No studies have focussed on the efficacy of such measures aimed at the population of older patients at large. Programmatic screening of the general population ('case finding on a systematic basis') for individuals at high risk of cardiovascular disease is an enormous logistic operation and, although more or less recommended by the current Dutch guideline, is still in its infancy in the Netherlands.[26] Against this background, various political parties, social organisations, pressure groups and older individuals themselves plea for the development of preventive institutions, such as 'preventive health centers for seniors', exclusively aimed at older people. Other (semi-) commercial organisations, such as health insurance companies and home care organisations, have discovered this niche in the market and acted accordingly. At present, loco-regional initiatives therefore have resulted in the development of some 90 'health centers for seniors' throughout the country (situation October 2008).[27] In all these centers, screening for cardiovascular disease and its classic risk factors is a main area of interest during visits of older people, aged 50 and over. Blood pressure,

cholesterol levels, body mass index and blood glucose levels are routinely measured, and patients are referred to their general practitioner when abnormal values are measured. Thus far, however, it is still unclear whether these primary preventive measurements in old age are evidence-based, principally in those aged 75 years and over.

In conclusion: prevention of cardiovascular disease in old age increasingly attracts attention from all parties involved. While evidence for secondary prevention in old age is fairly robust, older patients are frequently undertreated. Conversely, for primary prevention in old age evidence is largely nonexistent, yet primary preventive initiatives for older people are booming.

1.3 Cardiovascular risk prediction in old age

1.3a Classic risk factors

For decades risk prediction for cardiovascular disease was based on the concept of 'risk factors': people with for instance high blood pressures had more cardiovascular events than people with normal blood pressures, and when these high blood pressures were lowered through effective interventions (such as antihypertensive medication), the incidence of cardiovascular events also decreased.[28] So high systolic blood pressure was a bad prognostic sign. Similar reasoning was adapted for high total cholesterol and high low-density lipoprotein cholesterol levels, low high-density lipoprotein cholesterol levels, and body mass index. For the risk factors male sex, smoking and diabetes the risk was dichotomised: one either has the risk factor, or one has not. During the 90s of the previous century, evidence was emerging from observational cohort studies that the prognostic value of these individual risk factors were waning with increasing age: in the oldest old a low total cholesterol level was a predictor of higher mortality, and the same applies to low systolic blood pressure, that also predicts greater cardiovascular mortality and morbidity.[29-33] However, randomised clinical trials concerning cholesterol lowering in high-risk older patients, as well as blood pressure lowering in older patients with hypertension still revealed positive results with regard to total mortality and (recurrent) cardiovascular morbidity.[13;15] Another, more comprehensive intervention in very old high-risk patients failed to produce positive outcomes, though risk factors were neatly reduced.[34] Interpretation of these seemingly conflicting data is not straightforward and should include assessment of internal validity and generalizability of the various studies. From a perspective of risk prediction, however, it is obvious that established risk factors in middle-aged patients are not automatically suitable for risk prediction in old age.

1.3b Cardiovascular risk scores

The first paper on the well-known Framingham Heart Study goes back to 1949, when the principal investigators described the aims and the design of the study.[35] It was the first of a total of 1866 articles (1951-2007) based on this landmark observational study, which included three generations of participants thus far (www.framinghamheartstudy.com, accessed 24 December 2008). It has led to an increasing understanding of the determinants of cardiovascular disease, and worldwide its outcomes have been cited and

applied. One of the merits of this study was the development of a risk score for people without known cardiovascular disease: the Framingham risk score.[36;37] This instrument weighs each of the classic risk factors, and in doing so calculates an individual risk of developing coronary heart disease in the next 10 years. This was a shift of concept: from evaluation and treatment of separate risk factors to a more integrated approach evaluating the global cardiovascular risk. During the decades that followed, several other risk scores have been introduced, which either included different or additional risk factors, were calibrated for different geographical populations, or used different outcomes (e.g. 'cardiovascular mortality' versus 'coronary heart disease'). Anyhow, their common backbone comprises established classic risk factors.[38-40] In view of earlier remarks about the predictive value of these risk factors in old age, serious concerns about the value of these risk scores in older patients are justified.

1.3c New biomarkers

Although middle-aged people with (aggregations of) classic risk factors have high risks of developing cardiovascular disease, even in these age groups an important fraction of incident cardiovascular disease occurs in people without any classic risk factor.[41] This explains the ongoing search for a new type of marker of cardiovascular risk, often called 'biomarkers', over the last few decades. Indeed, a seemingly endless list of new biomarkers for cardiovascular disease has emerged, which can be grouped into markers of inflammation, endothelial dysfunction and oxidative stress, cardiac injury markers, markers of neurohumoral activation, renal injury markers, procoagulant markers, dyslipidaemic markers and glycaemic markers.[42;43] This growing interest for biomarkers is also illustrated by two MEDLINE searches (date of entry 14 February 2009), restricted to two different calendar years with a 10-year interval. A search with the MeSH terms 'biological markers' and 'cardiovascular disease', restricted to the year 1998, results in 1498 articles, of which 227 reviews, and when restricted to the year 2008 this number more than doubles: 3573 articles, of which 496 reviews. For the majority of the aforementioned biomarkers strong associations with cardiovascular disease and mortality have been established in middle-aged populations, and for some also in old age.[44-49] In middle-aged populations, the principal question when evaluating new biomarkers' values is whether (combinations of) biomarkers add prognostic value *beyond* classic risk factors. Although some researchers have claimed significant outcomes in this respect, overall assessment of this incremental value of various biomarkers has been disappointing, and none of the new biomarkers to date is used in daily practice of risk prediction.[43;50-54] However, in older populations the prognostic value of the classic risk factors themselves is waning with age, as described in paragraph 1.3a, and the search for new and prognostic powerful biomarkers therefore is even more relevant: they may not only be useful in addition to the classic risk factors, but may well replace them, and thus fill the gap that classic risk factors create in old age. Until now, only fragmentary data on the potential of various new biomarkers in older populations are available.

In conclusion, in cardiovascular risk prediction in older patients without history of cardiovascular disease, there are many indications that established classic risk factors might not qualify for adequate risk prediction, and, as a result, the same applies to existing risk scores. This underscores the importance of the ongoing search for robust new markers of cardiovascular risk in old age.

1.4 Aims of this thesis and brief description of chapters

The general aim of this thesis is to study cardiovascular risk management in old age, in order to facilitate the development of age-specific and evidence-based guidelines for this age group. The thesis is divided in three parts, which are described below.

Part 1 Current cardiovascular prevention in old age

The first part (chapters 2 and 3) describes the status quo of cardiovascular prevention in older patients in the Netherlands and the role of general practitioners in this respect. Chapter 2 focuses on time trends from 2000-2007 in secondary prevention of cardiovascular disease after a prior myocardial infarction, in different age groups from age 65 years onwards. Secondary prevention by appropriate life style changes and secondary preventive medication is widely considered standard treatment nowadays, also in old age.[18] As guidelines on this matter have changed according to availability of evidence, in this chapter it was tested whether improvements have occurred over time. Chapter 3 describes a qualitative and quantitative study into the attitude of general practitioners in the Netherlands towards prevention of cardiovascular disease in old age and their current activities in this respect, as well as the barriers they encounter with these preventive activities. Results of focus group interviews with general practitioners, as well as results from a nationwide survey are presented.

Part 2 The value of routine ECGs in older persons from the general population

The second part (chapters 4 and 5) focuses on the routine-electrocardiogram in older patients as a prognostic instrument for mortality and cardiovascular morbidity, and evaluates its added value beyond readily available information from the medical record. Chapter 4 describes the prognostic value regarding mortality and functional status of prior myocardial infarction and atrial fibrillation on routine-ECGs in participants from the Leiden 85-plus Study, and evaluates whether this relatively simple diagnostic procedure could be an effective screening tool to select people with high mortality risks or risk of accelerated functional decline. In chapter 5 the prognostic qualities of routine-ECGs in very old patients are compared with information about these patients' cardiovascular history from the medical records. It covers the question whether routine-ECGs still add valuable information beyond what is already known by the general practitioner.

Part 3 Primary prevention of cardiovascular disease in old age
The third part (chapters 6 to 9) of this thesis is aimed at primary prevention in old age, and entails an assessment of the prognostic performance in old age of classic cardiovascular risk factors, followed by various studies into the prognostic value of new biomarkers of cardiovascular disease. Chapter 6 studies the prognostic value of the classic risk factors for cardiovascular disease (systolic hypertension, smoking, total and HDL-cholesterol levels, diabetes, left ventricular hypertrophy on the ECG) and compares them with the prognostic value of several new biomarkers. Classic risk prediction in very old people without history of cardiovascular disease, using the Framingham risk score (including all classic risk factors), is compared with risk prediction based on four new biomarkers available from the Leiden 85-plus Study: homocysteine, folic acid, interleukin-6 and C-reactive protein. Chapter 7 is based on research within the Rotterdam Study and elaborates on the findings in chapter 6, looking into the mortality risks that are associated with different (systolic) blood pressures, depending on factual age of the older persons. An attempt is made to establish the break-even point: at what age does high blood pressure change from a genuine risk factor into a favourable prognostic sign? This chapter also includes a discussion on the necessity to develop age-dependent guidelines concerning primary prevention of cardiovascular disease in older persons. Chapters 8 and 9 deal with the value of another biomarker: (N-terminal pro-) brain natriuretic peptide. This biomarker was first detected in pig brains, but in humans it was soon recognized as a cardiac marker of left ventricular wall stress, and as such, a very sensitive, but not very specific, marker of heart failure.[55] Chapter 8 is a systematic review into the diagnostic accuracy of natriuretic peptides for cardiac dysfunction and chronic heart failure in old age. In chapter 9, the value of NT-proBNP as predictor of total mortality and cause-specific mortality is evaluated in a cohort of 90-year olds from the Leiden 85-plus Study.

Final chapters
Chapter 10 is a general discussion of the main findings from this thesis, and includes clinical implications and directions for future research. Chapter 11 summarizes all chapters; chapter 12 contains a summary in Dutch.

References

1. Vaartjes I, Peters RJG, Van Dis SJ, Bots ML. Cardiovascular disease in the Netherlands 2007. Den Haag (the Netherlands): Netherlands Heart Foundation, 2007.
2. Graham I, Atar D, Borch-Johnsen K, Boysen G, Burell G, Cifkova R et al. European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Eur Heart J 2007;28(19):2375-2414.
3. Lloyd-Jones D, Adams R, Carnethon M, De Simone G, Ferguson TB, Flegal K et al. Heart Disease and Stroke Statistics--2009 Update. A Report From the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2009;119(3):480-486.
4. Petersen S, Peto V, Rayner M, Leal J, Luengo-Fernandez R, Gray A. European cardiovascular disease statistics. London, British Heart Foundation, 2005.

5. Wellenius GA, Mittleman MA. Disparities in myocardial infarction case fatality rates among the elderly: The 20-year Medicare experience. Am Heart J 2008;156(3):483-490.
6. McKenna MT, Michaud CM, Murray CJL, Marks JS. Assessing the Burden of Disease in the United States Using Disability-Adjusted Life Years. Am J Prev Med 2005;28(5):415-423.
7. Garssen J. Bevolkingstrends. Statisch kwartaalblad over de demografie van Nederland. Jaargang 56, 4e kwartaal 2008. Den Haag/Heerlen, Centraal Bureau voor de Statistiek (Statistics Netherlands), 2008.
8. Bonow RO, Smaha LA, Smith SC, Mensah GA, Lenfant C. World Heart Day 2002 - The international burden of cardiovascular disease: Responding to the emerging global epidemic. Circulation 2002;106(13):1602-1605.
9. Smith SC, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC et al. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update - Endorsed by the National Heart, Lung, and Blood Institute. Circulation 2006;113(19):2363-2372.
10. Kerr AJ, Broad J, Wells S, Riddell T, Jackson R. Should the first priority in cardiovascular risk management be those with prior cardiovascular disease? Heart 2009;95(2):125-129.
11. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002;360(9326):7-22.
12. Afilalo J, Duque G, Steele R, Jukema JW, de Craen AJM, Eisenberg MJ. Statins for Secondary Prevention in Elderly Patients: A Hierarchical Bayesian Meta-Analysis. J Am Coll Cardiol 2008;51(1):37-45.
13. Beckett NS, Peters R, Fletcher AE, Staessen JA, Liu L, Dumitrascu D et al. Treatment of Hypertension in Patients 80 Years of Age or Older. N Engl J Med 2008;358(18):1887-1898.
14. Ratnasabapathy Y, Lawes CMM, Anderson CS. The perindopril protection against recurrent stroke study (PROGRESS) - Clinical implications for older patients with cerebrovascular disease. Drugs Aging 2003;20(4):241-251.
15. Shepherd J, Blauw GJ, Murphy MB, Bollen ELEM, Buckley BM, Cobbe SM et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. Lancet 2002;360(9346):1623-1630.
16. Watson K, Fung CH, Budoff M. Quality indicators for the care of ischemic heart disease in vulnerable elders. J Am Geriatr Soc 2007;55 Suppl 2:S366-S372.
17. Yusuf S. Two decades of progress in preventing vascular disease. Lancet 2002; 360(9326):2-3.
18. Williams MA, Fleg JL, Ades PA, Chaitman BR, Miller NH, Mohiuddin SM et al. Secondary Prevention of Coronary Heart Disease in the Elderly (With Emphasis on Patients >=75 Years of Age): An American Heart Association Scientific Statement From the Council on Clinical Cardiology Subcommittee on Exercise, Cardiac Rehabilitation, and Prevention. Circulation 2002;105(14):1735-1743.
19. DeWilde S, Carey IM, Richards N, Whincup PH, Cook DG. Trends in secondary prevention of ischaemic heart disease in the UK 1994 2005: use of individual and combination treatment. Heart 2008;94(1):83-88.
20. McCormick D, Gurwitz JH, Lessard D, Yarzebski J, Gore JM, Goldberg RJ. Use of aspirin, beta-blockers, and lipid-lowering medications before recurrent acute myocardial infarction: missed opportunities for prevention? Arch Intern Med 1999;159(6):561-567.
21. Setoguchi S, Glynn RJ, Avorn J, Levin R, Winkelmayer WC. Ten-Year Trends of Cardiovascular Drug Use After Myocardial Infarction Among Community-Dwelling Persons >=65 Years of Age. Am J Cardiol 2007;100(7):1061-1067.
22. Tran CTT, Laupacis A, Mamdani MM, Tu JV. Effect of age on the use of evidence-based therapies for acute myocardial infarction. Am Heart J 2004;148(5):834-841.
23. Summerskill WS, Pope C. 'I saw the panic rise in her eyes, and evidence-based medicine went out of the door.' An exploratory qualitative study of the barriers to secondary prevention in the management of coronary heart disease. Fam Pract 2002;19(6):605-610.
24. Putnam W, Twohig PL, Burge FI, Jackson LA, Cox JL. A qualitative study of evidence in primary care: what the practitioners are saying. CMAJ 2002;166(12):1525-1530.
25. Rose G. Strategy of prevention: lessons from cardiovascular disease. BMJ (Clin Res Ed) 1981;282(6279):1847-1851.
26. Burgers JS, Simoons ML, Hoes AW, Stehouwer CD, Stalman WA. [Guideline 'Cardiovascular Risk Management']. Ned Tijdschr Geneeskd 2007;151(19):1068-1074.
27. Visser G, Schippers A. The Health Care Center for Seniors. An inventarisation of fifteen health care centers for seniors. Utrecht, the Netherlands, NIZW Zorg, 2005.

28. Lenfant C, Chobanian AV, Jones DW, Roccella EJ. Seventh report of the Joint National Committee on the Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7): resetting the hypertension sails. Hypertension 2003;41(6):1178-1179.
29. Bemmel T, Gussekloo J, Westendorp RG, Blauw GJ. In a population-based prospective study, no association between high blood pressure and mortality after age 85 years. J Hypertens 2006;24(2):287-292.
30. Boshuizen HC, Izaks GJ, van Buuren S, Ligthart GJ. Blood pressure and mortality in elderly people aged 85 and older: community based study. BMJ 1998;316(7147):1780-1784.
31. Oates DJ, Berlowitz DR, Glickman ME, Silliman RA, Borzecki AM. Blood Pressure and Survival in the Oldest Old. J Am Geriatr Soc 2007;55(3):383-388.
32. Rastas S, Pirttila T, Viramo P, Verkkoniemi A, Halonen P, Juva K et al. Association between blood pressure and survival over 9 years in a general population aged 85 and older. J Am Geriatr Soc 2006;54(6):912-918.
33. Weverling-Rijnsburger AW, Blauw GJ, Lagaay AM, Knook DL, Meinders AE, Westendorp RG. Total cholesterol and risk of mortality in the oldest old. Lancet 1997;350(9085):1119-1123.
34. Strandberg TE, Pitkala KH, Berglind S, Nieminen MS, Tilvis RS. Multifactorial intervention to prevent recurrent cardiovascular events in patients 75 years or older: The Drugs and Evidence-Based Medicine in the Elderly (DEBATE) study: A randomized, controlled trial. Am Heart J 2006;152(3):585-592.
35. Dawber TR, Meadors GF, Moore FE, Jr. Epidemiological approaches to heart disease: the Framingham Study. Am J Public Health Nations Health 1951;41(3):279-281.
36. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular-Disease Risk Profiles. Am Heart J 1991;121(1):293-298.
37. Anderson KM, Wilson PWF, Odell PM, Kannel WB. An Updated Coronary Risk Profile - A Statement for Health-Professionals. Circulation 1991;83(1):356-362.
38. Conroy RM, Pyorala K, Fitzgerald AP, Sans S, Menotti A, De Backer G et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J 2003;24(11):987-1003.
39. Hippisley-Cox J, Coupland C, Vinogradova Y, Robson J, May M, Brindle P. Derivation and validation of QRISK, a new cardiovascular disease risk score for the United Kingdom: prospective open cohort study. BMJ 2007;335(7611):136.
40. Woodward M, Brindle P, Tunstall-Pedoe H. Adding social deprivation and family history to cardiovascular risk assessment: the ASSIGN score from the Scottish Heart Health Extended Cohort (SHHEC). Heart 2007;93(2):172-176.
41. Lauer MS. Primary Prevention of Atherosclerotic Cardiovascular Disease: The High Public Burden of Low Individual Risk. JAMA 2007;297.
42. Scott IA. Evaluating cardiovascular risk assessment for asymptomatic people. BMJ 2009;338(jan05_1):a2844.
43. Myers GL, Christenson RH, Cushman M, Ballantyne CM, Cooper GR, Pfeiffer C et al. National Academy of Clinical Biochemistry Laboratory Medicine Practice Guidelines: Emerging Biomarkers for Primary Prevention of Cardiovascular Disease. Clin Chem 2009;55(2):378-384.
44. Humphrey LL, Rongwei FU, Rogers KEVI, Freeman MICH, Helfland MARK. Homocysteine Level and Coronary Heart Disease Incidence: A Systematic Review and Meta-analysis. Mayo Clinic Proceedings 2008;83(11):1203-1212.
45. Daniels LB, Laughlin GA, Sarno MJ, Bettencourt R, Wolfert RL, Barrett-Connor E. Lipoprotein-Associated Phospholipase A2 Is an Independent Predictor of Incident Coronary Heart Disease in an Apparently Healthy Older Population: The Rancho Bernardo Study. J Am Coll Cardiol 2008;51(9):913-919.
46. Kistorp C, Raymond I, Pedersen F, Gustafsson F, Faber J, Hildebrandt P. N-Terminal Pro-Brain Natriuretic Peptide, C-Reactive Protein, and Urinary Albumin Levels as Predictors of Mortality and Cardiovascular Events in Older Adults. JAMA 2005;293(13):1609-1616.
47. Strandberg TE, Tilvis RS. C-Reactive Protein, Cardiovascular Risk Factors, and Mortality in a Prospective Study in the Elderly. Arterioscler Thromb Vasc Biol 2000;20(4):1057-1060.
48. van der Steeg WA, Boekholdt SM, Stein EA, El Harchaoui K, Stroes ESG, Sandhu MS et al. Role of the Apolipoprotein B-Apolipoprotein A-I Ratio in Cardiovascular Risk Assessment: A Case-Control Analysis in EPIC-Norfolk. Ann Intern Med 2007;146(9):640-648.

49. Zethelius B, Berglund L, Sundstrom J, Ingelsson E, Basu S, Larsson A et al. Use of Multiple Biomarkers to Improve the Prediction of Death from Cardiovascular Causes. N Engl J Med 2008;358(20):2107-2116.
50. de Lemos JA. The Latest and Greatest New Biomarkers: Which Ones Should We Measure for Risk Prediction in Our Practice? Arch Intern Med 2006; 166(22):2428-2430.
51. Ware JH. The Limitations of Risk Factors as Prognostic Tools. N Engl J Med 2006;355(25):2615-2617.
52. Wang TJ, Gona P, Larson MG, Tofler GH, Levy D, Newton-Cheh C et al. Multiple Biomarkers for the Prediction of First Major Cardiovascular Events and Death. N Engl J Med 2006;355(25):2631-2639.
53. Gotto J. Role of C-Reactive Protein in Coronary Risk Reduction: Focus on Primary Prevention. Am J Cardiol 2007;99(5):718-725.
54. Danesh J, Wheeler JG, Hirschfield GM, Eda S, Eiriksdottir G, Rumley A et al. C-Reactive Protein and Other Circulating Markers of Inflammation in the Prediction of Coronary Heart Disease. N Engl J Med 2004;350(14):1387-1397.
55. Hobbs FD, Davis RC, Roalfe AK, Hare R, Davies MK, Kenkre JE. Reliability of N-terminal pro-brain natriuretic peptide assay in diagnosis of heart failure: cohort study in representative and high risk community populations. BMJ 2002;324(7352):1498.