



New guidelines for the prevention of cardiovascular disease

KRONIKK

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New national guidelines for the prevention of cardiovascular disease include a novel algorithm that calculates the risk of cardiovascular events and death. The guidelines contain updated recommendations with which health care professionals should familiarise themselves.

The revised guidelines have recently been published on the website of the Norwegian Directorate of Health and consist of 20 recommendations (1). They replace the existing national guidelines for individual primary prevention of cardiovascular disease issued by the Directorate in 2009 (2). The latter contained advice on lifestyle changes and principles of pharmacological prevention. They also included a risk chart (NORRISK) for ten-year cardiovascular mortality risk for persons aged 40–70 years (2, 3), and recommended age-specific thresholds for pharmacological intervention (4).

Risk factors for cardiovascular disease, and levels of morbidity and mortality due to cardiovascular disease, have changed considerably within the population over the past 5–10 years, with reductions in cholesterol and blood pressure levels, and in the number of daily smokers (5, 6). Clinical studies in primary prevention have helped clarify the effects of pharmacotherapy in cases of intermediate cardiovascular risk (7–9). In both the UK and the USA, new guidelines have been published on the basis of these findings, which recommend primary prevention with statins at a lower risk level than before (10, 11). The intervention threshold has not, however, been adjusted in the latest joint European guidelines (12).

Knowledge acquisition and working processes

There is demand among health care professionals in Norway for a risk calculator for cardiovascular events as opposed to merely cardiovascular mortality. There is also demand for guidelines on secondary prevention in general, for guidelines on primary and secondary prevention in the over 70s, and for guidance on prevention in the oldest old. In autumn 2014, the Directorate of Health appointed a committee to revise the existing guidelines, starting with the group that authored the guidelines in 2009. Additional candidates were invited to ensure a balanced composition with respect to gender, research experience, geographical affiliation and clinical experience within the primary and specialist health

care services.

The most important new elements in cardiovascular preventive medicine were identified by reviewing recent international guidelines (10–12). Non-systematic literature searches were also conducted. Systematic literature searches for acetylsalicylic acid, treatment of hypertension, and statins were performed to identify recommendations for pharmaceutical prophylaxis in the over 70s.

NORRISK 2

Developing a new tool for calculating cardiovascular risk required access to extensive epidemiological data, with in-depth statistical analysis and validation (13). The model is based on the Cohort of Norway health surveys (CONOR) (14), linked to the CVDNOR project, which recorded cardiovascular-related causes of death and discharge diagnoses in Norwegian hospitals in the period 1994–2009 (15). NORRISK 2 presents the ten-year risk of acute non-fatal or fatal stroke or myocardial infarction, or death from coronary artery disease. Gender, age, smoking habits, systolic blood pressure and total cholesterol are included in the model as before, but with the addition of HDL cholesterol, myocardial infarction in a first-degree relative before the age of 60, and medically controlled hypertension. The new model also takes into account the competing risk of death. The age categories have been raised by five years, with separate intervention thresholds for the categories 45–54 years, 55–64 years and 65–74 years. This is because estimated risk very rarely exceeds the intervention threshold in those under 45 years of age, while a greater number of healthy elderly persons aged 69–74 years are now candidates for primary prevention. An electronic risk calculator has been developed in addition to the risk chart.

KNOWLEDGE BASE AND CLINICAL CONSIDERATIONS

The committee emphasised the need to strike a balance between overtreatment and medicalisation of healthy persons versus undertreatment and lost opportunities for prevention. The recommendations on assessment and studies of lipid disorders, hypertension and overall cardiovascular risk also emphasise the need to limit the use of resources. There is thus a restrictive approach to repeated sampling (e.g. of blood cholesterol) and to the use of various methods for additional risk determination, which often have insufficient documentation (16). Problems associated with overdiagnosis in Norwegian medical practice have been discussed recently in this journal (17).

Important changes and new items

The new guidelines cover the evaluation of cardiovascular risk, lipid disorders and hypertension, the characterisation of lifestyle habits and advice on lifestyle interventions, and the use of drugs in primary and secondary prevention. Recommendations are also made regarding the prevention of cardiovascular disease in the over 75s. A selection of key points and changes from 2009 are listed in Table 1.

Table 1

Schematic overview of key recommendations from the new guidelines regarding primary prevention of cardiovascular disease, with comparison of the 2009 and 2017 versions

Recommendation	2009	2017
Risk assessment	NORRISK Ten-year risk of cardiovascular mortality	NORRISK 2 Ten-year risk of cardiovascular morbidity and mortality

Recommendation	2009	2017
Intervention threshold for medical prophylaxis (statin and/or treatment of hypertension)	In the event of risk: ≥ 1% in age group 40–49 years ≥ 5% in age group 50–59 years ≥ 10% in age group 60–69 years	In the event of risk: ≥ 5% in age group 45–54 years ≥ 10% in age group 55–64 years ≥ 15% in age group 65–74 years
24-hour blood pressure (BP)	Upon indication	Use recommended in risk assessment. Increased risk associated with 24-hour blood pressure (BP) ≥ 130/80 mm Hg
Individual factors/criteria that trigger recommendation for pharmacotherapy (independent of calculated risk)		
Total cholesterol LDL cholesterol	≥ 8.0 mmol/l Not specified (except in postmenopausal women without other risk factors)	≥ 7.0 mmol/l ≥ 5.0 mmol/l (except in postmenopausal women without other risk factors)
Systolic blood pressure Diastolic blood pressure Hypertension-induced end-organ damage	≥ 160 mm Hg ≥ 100 mm Hg End-organ damage	≥ 160 mm Hg ≥ 100 mm Hg End-organ damage
Diabetes 1 and 2, age > 40 years	Risk-dependent	Standard treatment with initiation of atorvastatin 20 mg (independent of risk when LDL cholesterol > 2.5 mmol/l)
Guideline target blood pressure	< 140/90 mm Hg (GP surgery measurements)	< 140/90 mm Hg (GP surgery measurements) 140–150 mm Hg systolic BP for over-80s
Guideline treatment target/ Recommended standard treatment lipids	Total cholesterol < 5.0 mmol/l LDL cholesterol < 3.0 mmol/l	Standard treatment with initiation of atorvastatin 20 mg. Guideline target LDL cholesterol < 3.0 mmol/l (< 2.5 mmol/l in cases of diabetes and familial hyperlipidemia)

ADVICE ON LIFESTYLE INTERVENTIONS

Advice on lifestyle interventions forms the basis for prevention of cardiovascular disease. The revised guidelines focus on the particular circumstances relevant to persons diagnosed with cardiovascular disease or at especially high risk of such disease. Help with smoking cessation is the most important intervention, and the guidelines recommend offering assistance to all those who still smoke, including smoking-cessation medications. Smoking 'now and then' should be discouraged. It is recommended that patients who have been diagnosed with cardiovascular disease are offered the chance to participate in a structured cardiac rehabilitation programme.

HOW TO USE THE NEW RISK CHART

The new risk chart, NORRISK 2, is shown in Figure 1. As well as age, gender, smoking habits, systolic blood pressure and total cholesterol, NORRISK 2 recommends consideration of additional risk factors. These are listed in Table 2 with the recommended multiplication factor for risk adjustment. The Directorate of Health's website features a risk calculator, into which standard risk factors – and three others included in the new model (low HDL cholesterol, familial risk and ongoing hypertension treatment) – can be entered to calculate an overall risk score. For the remaining factors in Table 2, a further 'manual' adjustment

must be made at the end.

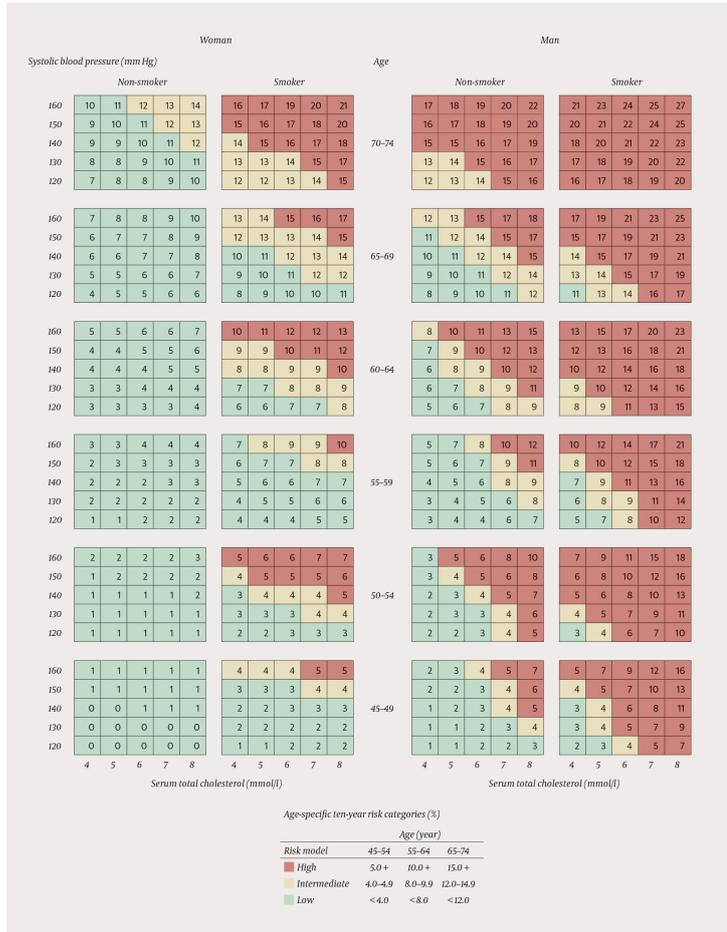


Figure 1 NORRISK 2 risk model. Ten-year risk of non-fatal or fatal myocardial infarction or stroke or death from coronary artery disease, given the absence of familial risk, low HDL cholesterol and medically treated hypertension (1). Risk estimates are based on the average age within each age group.

Table 2

Key factors that should be studied for comprehensive risk assessment (1)

Additional factor	Recommended multiplication factor
Included in risk calculation:	
Additional factor	Recommended multiplication factor
Myocardial infarction under the age of 60 in a first-degree relative	1.3
Myocardial infarction under the age of 60 in two or more first-degree relatives	1.7
Medically treated hypertension	1.3
Low HDL-cholesterol (i.e. < 1.0 mmol/l for men, < 1.3 mmol/l for women)	1.4
Further additional factors:	
South Asian ethnicity	1.5
Rheumatoid arthritis	1.4
Abdominal obesity (i.e. > 88 cm for women, > 100 cm for men)	Discretionary
Psychosocial load and stress	Discretionary
Depression, medication-controlled psychotic illness	Discretionary

HOW SHOULD THE INTERVENTION THRESHOLD BE DEFINED?

If advice on changes in lifestyle habits has had insufficient effect after 3–12 months, the revised guidelines recommend offering pharmaceutical intervention in cases where the calculated risk of a cardiovascular event is $\geq 5\%$ for the age group 45–54 years, $\geq 10\%$ for the age group 55–64 years and $\geq 15\%$ for the age group 65–74 years.

The principle of age-specific intervention thresholds has been retained from 2009, both to optimise sensitivity and specificity (13, 18) (Table 3) and to ensure that the number of persons for whom intervention is recommended is manageable for the primary health care service. Based on figures from the seventh Tromsø Study (Tromsø 7) (2015–16), the working group has estimated that approximately 750 000 persons in Norway aged 45–74 years will fulfil the criteria for pharmacotherapy (19). Most of these are already on treatment, either due to established cardiovascular disease or because their blood pressure or cholesterol levels per se necessitate treatment (Table 4). A minority, approximately 110 000 persons, will qualify for treatment only because their risk score exceeds the recommended intervention threshold (primary prevention). The total number of persons requiring treatment is estimated to be about the same as at present.

Table 3

Sensitivity and specificity of different intervention thresholds in the model population (HUNT 2, Tromsø 4 and HUSK). Sensitivity: Percentage with a calculated risk score above threshold among those who subsequently suffered acute myocardial infarction or stroke within ten years. Specificity: Percentage with a calculated risk score below threshold among those who did not suffer acute myocardial infarction or stroke within 10 years. Low intervention thresholds capture most of those who would have gone on to experience myocardial infarction or stroke: sensitivity is high. However, many individuals who would not have experienced an event within the next ten years, even without intervention, will also be included: specificity is low. The aim is to provide effective treatment for persons with clearly increased risk while avoiding the medicalisation of large parts of the population. The thresholds selected, 5%, 10% and 15%, are an attempt to balance sensitivity and specificity. The thresholds are harmonised to work well together for men and women, but the table shows that there are clear gender differences

Age	Men			Women		Men + women	
	Threshold (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity	Specificity
45–54	2	98	9	72	62	90	37
	4	84	44	37	88	70	67
	5	73	57	25	93	59	76
	7	56	76	11	97	42	87
Age	Men			Women		Men + women	
	Threshold (%)	Sensitivity (%)	Specificity (%)	Sensitivity (%)	Specificity (%)	Sensitivity	Specificity
55–64	8	48	81	7	98	36	90
	5	99	6	85	43	94	26
	7	94	21	60	66	81	45
	8	90	29	53	73	76	53
	10	78	46	40	84	64	66
	12	62	61	25	91	48	77
65–74	10	100	2	91	21	96	13
	12	98	6	80	38	90	25
	15	90	19	57	62	75	43
	20	60	53	28	86	46	72

Table 4

Cumulative percentage on treatment when the guidelines are applied to data from Tromsø 7 (per cent/number of persons). (The table shows how many would potentially be treated under the proposed criteria based on the most recent Tromsø Study. The first column shows the percentage who reported during the study that they had diabetes. These patients will be followed up in accordance with separate guidelines. About 10–11% of the men are considered for treatment only because of a high risk score. The proportion is markedly lower for women, reflecting the fact that the ten-year risk in women is relatively low in these age groups)

N	Diabetes	Cardiovascular disease ¹	Using blood pressure medications ²	Using statins ³	Systolic blood pressure \geq 160 mm Hg ⁴	Total cholesterol \geq threshold ⁵	Risk \geq threshold ⁶	Total excluding diabetes	Population in Norway 2015	Number potentially treated	Of these, only due to risk	
Women												
45 – 54	3529	2.2	4.6	6.2	1.5	1.3	1.4	1.0	16.0	344 481	54 957	3 514
55 – 64	2759	4.0	7.2	15.3	4.8	3.5	0.0	1.4	32.2	298 018	96 027	4 213
65 – 74	1881	6.0	11.3	25.7	7.7	6.1	0.0	2.4	53.2	241 041	128 145	5 767
Men												
45 – 54	2880	3.8	6.7	7.6	2.8	2.7	6.9	11.0	37.8	365 409	138 043	40 220
55 – 64	2506	4.9	14.6	15.1	3.5	4.3	5.7	9.6	52.8	305 180	161 115	29 349
65 – 74	1885	8.8	24.3	24.5	3.6	4.8	2.7	11.4	71.2	233 524	166 378	26 635
											744	109
											665	698

LOWER THRESHOLDS FOR CHOLESTEROL

Since the 1970s, cholesterol levels in the population have decreased by 1–1.5 mmol/l (5, 6, 20), including in persons with an underlying genetic lipid disorder. Whereas total cholesterol \geq 8.0 mmol/l was previously thought to indicate a familial lipid disorder, today anyone with total cholesterol \geq 7.0 mmol/l and/or LDL cholesterol \geq 5.0 mmol/l is highly likely to have such a disorder. These individuals will have a greater disease risk than their cholesterol level would otherwise suggest because their lipid level may have been elevated from a young age. The new guidelines therefore recommend offering statins for primary prevention to persons aged $<$ 75 with total cholesterol \geq 7.0 mmol/l (as opposed to \geq 8.0 mmol/l previously, provided that LDL cholesterol \geq 5.0 mmol/l), but also to those with LDL cholesterol \geq 5.0 mmol/l and total cholesterol $<$ 7.0 mmol/l. An important exception is women who develop such cholesterol levels *after* the menopause and who have no other risk factors. Reducing the threshold from \geq 8.0 mmol/l to \geq 7.0 mmol/l would, according to similar calculations (Table 4), lead to approximately 25 000 more people becoming eligible for treatment.

24-HOUR BLOOD PRESSURE MONITORING

The new guidelines recommend a low threshold for using 24-hour blood pressure monitoring to ensure a correct diagnosis of hypertension. This is especially important in healthy persons without detectable organ damage.

TREATMENT TARGETS AND STANDARD TREATMENT

For primary prevention, initiation of atorvastatin 20 mg x 1 is recommended as standard cholesterol-lowering therapy. This will have a good prophylactic effect in the vast majority of patients, and there is insufficient evidence to support the use of specific treatment targets to manage therapy (11). For secondary prevention, LDL cholesterol $<$ 1.8 mmol/l is recommended as a treatment target, in line with international recommendations (11, 12).

The main classes of anti-hypertensive drugs (apart from beta-blockers) are now seen as

being of equal value for lowering blood pressure, and the choice of drug will be dictated by additional indications, side effects and contraindications. The new guidelines specify a target blood pressure of <140/90 mm Hg for all patient groups, both in primary and secondary prevention. A somewhat lower treatment target may be considered for patients with diabetes or stroke, while systolic blood pressure of 140–150 mm Hg should be the target for persons aged over 80 years.

As in European guidelines, acetylsalicylic acid is recommended for primary prevention only in exceptional cases (9, 12).

PRINCIPLES OF SECONDARY PREVENTION

The guidelines contain advice on treatment with lipid-lowering drugs, acetylsalicylic acid (or another platelet anti-aggregation agent), beta-blockers and ACE inhibitors (alternatively angiotensin receptor blockers) in the stable phase following diagnosis of coronary artery disease, ischaemic stroke or peripheral atherosclerosis. The recommendations provide general guidelines for which drugs to use and for how long, after various types of cardiovascular events. The treatment of hypertension in cases of known cardiovascular disease is also discussed.

TREATMENT IN THE ELDERLY

Extensive variation in health status is seen among the over 75s, and the use of prophylactic drugs must be adjusted to accommodate multimorbidity and polypharmacy.

Statin therapy is recommended as secondary prevention for the over 75s as for younger individuals, unless health status or life expectancy are markedly diminished. Statins should only be used for primary prevention, however, following an individual risk/benefit assessment. Ongoing statin therapy should be discontinued in the event of disease that reduces the expected therapeutic benefits, such as advanced cancer, malnutrition, organ failure or dementia.

Treatment of hypertension has a significant effect on the risk of cardiovascular endpoints also in the elderly (21, 22). However, treatment of frail elderly patients with markedly reduced life expectancy requires careful consideration, and treatment should similarly be reduced or discontinued when other serious conditions are present.

Implementation

The revised guidelines are a continuation of the existing guidelines, but with important adjustments to risk estimation and corresponding changes in the recommended intervention thresholds. Changing poor lifestyle habits remains central to disease prevention, but whether or not to offer additional pharmacological prevention is an important question that requires careful consideration of the patient's overall situation. The Directorate of Health's guidelines are normative documents, but health care professionals must exercise professional judgement when evaluating each individual patient.

We hope that the revised guidelines will be a useful tool for the prevention of cardiovascular disease which, despite major progress, remains the most common cause of death in Norway.

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