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New guidelines for the prevention of cardiovascular disease

PERSPECTIVES

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New national guidelines for the prevention of cardiovascular disease include a novel algorit 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 recommendations (1). They replace the existing national guidelines for individual primary prevention of cardiovascular 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 – (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 change considerably within the population over the past 5 – 10 years, with reductions in cholesterol and blood pressure levels, a number of daily smokers (5, 6). Clinical studies in primary prevention have helped clarify the effects of pharmacotherap of intermediate cardiovascular risk (7–9). In both the UK and the USA, new guidelines have been published on the basis findings, which recommend primary prevention with statins at a lower risk level than before (10, 11). The intervention th 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 t cardiovascular mortality. There is also demand for guidelines on secondary prevention in general, for guidelines on prin secondary prevention in the over 70s, and for guidance on prevention in the oldest old. In autumn 2014, the Directorate appointed a committee to revise the existing guidelines, starting with the group that authored the guidelines in 2009. Ad candidates were invited to ensure a balanced composition with respect to gender, research experience, geographical affi clinical experience within the primary and specialist health care services.

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

NORRISK 2

Developing a new tool for calculating cardiovascular risk required access to extensive epidemiological data, with in-dept statistical analysis and validation (13). The model is based on the Cohort of Norway health surveys (CONOR) (14), linke CVDNOR project, which recorded cardiovascular-related causes of death and discharge diagnoses in Norwegian hospita period 1994 – 2009 (15). NORRISK 2 presents the ten-year risk of acute non-fatal or fatal stroke or myocardial infarctio from coronary artery disease. Gender, age, smoking habits, systolic blood pressure and total cholesterol are included in as before, but with the addition of HDL cholesterol, myocardial infarction in a first-degree relative before the age of 60, medically controlled hypertension. The new model also takes into account the competing risk of death. The age categori been raised by five years, with separate intervention thresholds for the categories 45 – 54 years, 55 – 64 years and 65 – 7 This is because estimated risk very rarely exceeds the intervention threshold in those under 45 years of age, while a grea number of healthy elderly persons aged 69 – 74 years are now candidates for primary prevention. An electronic risk calc 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 v undertreatment and lost opportunities for prevention. The recommendations on assessment and studies of lipid disorde hypertension and overall cardiovascular risk also emphasise the need to limit the use of resources. There is thus a restri approach to repeated sampling (e.g. of blood cholesterol) and to the use of various methods for additional risk determin which often have insufficient documentation (16). Problems associated with overdiagnosis in Norwegian medical practi 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 habits and advice on lifestyle interventions, and the use of drugs in primary and secondary prevention. Recommendatio made regarding the prevention of cardiovascular disease in the over 75s. A selection of key points and changes from 20 listed in Table 1.

Table 1

Schematic overview of key recommendations from the new guidelines regarding primary prevention of cardiovascular disease, with 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 morbid mortality
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. risk associated with 24-hour blood pre 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 wi 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 a 20 mg (independent of risk when LDL > 2.5 mmol/l)
Guideline target blood pressure	< 140/90 mm Hg (GP surgery measurements)	< 140/90 mm Hg (GP surgery measure 140–150 mm Hg systolic BP for over-8
Guideline treatment target/ Recommended standard treatment lipids	Total cholesterol < 5.0 mmol/l LDL cholesterol < 3.0 mmol/l	Standard treatment with initiation of a 20 mg. Guideline target LDL cholester mmol/l (< 2.5 mmol/l in cases of diabe familial hyperlipidemia)

Advice on lifestyle interventions

Advice on lifestyle interventions forms the basis for prevention of cardiovascular disease. The revised guidelines focus o particular circumstances relevant to persons diagnosed with cardiovascular disease or at especially high risk of such dis with smoking cessation is the most important intervention, and the guidelines recommend offering assistance to all tho smoke, including smoking-cessation medications. Smoking 'now and then' should be discouraged. It is recommended th who have been diagnosed with cardiovascular disease are offered the chance to participate in a structured cardiac rehab 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 an cholesterol, NORRISK 2 recommends consideration of additional risk factors. These are listed in Table 2 with the recom multiplication factor for risk adjustment. The Directorate of Health's website features a risk calculator, into which stand factors – and three others included in the new model (low HDL cholesterol, familial risk and ongoing hypertension treat can be entered to calculate an overall risk score. For the remaining factors in Table 2, a further 'manual' adjustment mus at the end.

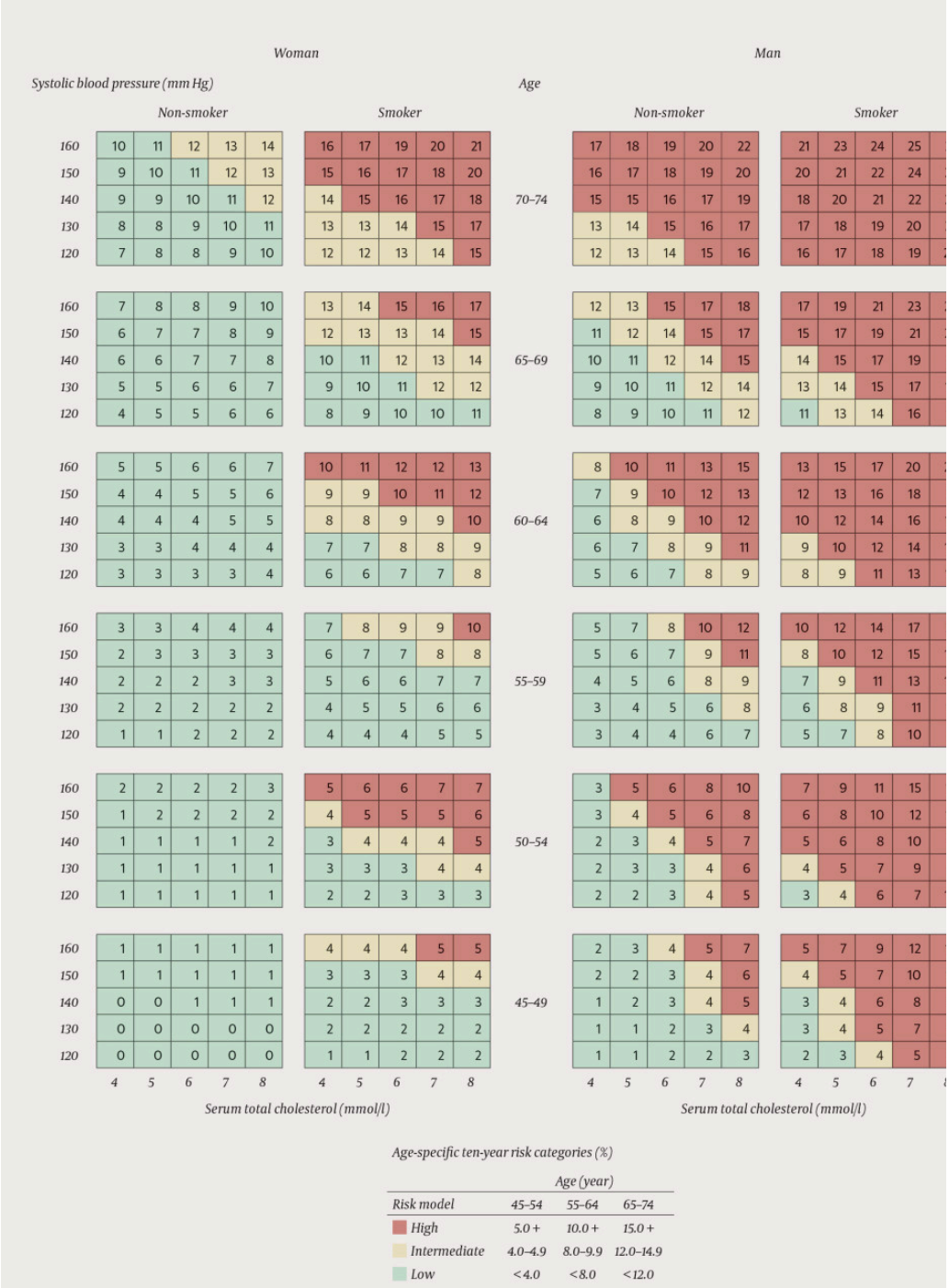

Figure 1 NORRISK 2 risk model. Ten-year risk of non-fatal or fatal myocardial infarction or stroke or death from coronary artery d
given the absence of familial risk, low HDL cholesterol and medically treated hypertension (1). Risk estimates are based on the aver
within each age group.

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 fa**
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

Additional factor	Recommended multiplication factor
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 pharmaceutical intervention in cases where the calculated risk of a cardiovascular event is ≥ 5 % for the age group 45 – 5 10 % for the age group 55 – 64 years and ≥ 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 spec 18) (Table 3) and to ensure that the number of persons for whom intervention is recommended is manageable for the pr health care service. Based on figures from the seventh Tromsø Study (Tromsø 7) (2015 – 16), the working group has esti approximately 750 000 persons in Norway aged 45 – 74 years will fulfil the criteria for pharmacotherapy (19). Most of th already on treatment, either due to established cardiovascular disease or because their blood pressure or cholesterol lev necessitate treatment (Table 4). A minority, approximately 110 000 persons, will qualify for treatment only because thei score exceeds the recommended intervention threshold (primary prevention). The total number of persons requiring tre 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: with a calculated risk score above threshold among those who subsequently suffered acute myocardial infarction or stroke within te Specificity: Percentage with a calculated risk score below threshold among those who did not suffer acute myocardial infarction or s 10 years. Low intervention thresholds capture most of those who would have gone on to experience myocardial infarction or stroke: is high. However, many individuals who would not have experienced an event within the next ten years, even without intervention, included: specificity is low. The aim is to provide effective treatment for persons with clearly increased risk while avoiding the medi large parts of the population. The thresholds selected, 5 %, 10 % and 15 %, are an attempt to balance sensitivity and specificity. The t are harmonised to work well together for men and women, but the table shows that there are clear gender differences

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

Table 4

Cumulative percentage on treatment when the guidelines are applied to data from Tromsø 7 (per cent/number of persons). (The tab how many would potentially be treated under the proposed criteria based on the most recent Tromsø Study. The first column shows percentage who reported during the study that they had diabetes. These patients will be followed up in accordance with separate gu About 10 – 11 % of the men are considered for treatment only because of a high risk score. The proportion is markedly lower for wo 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 ≥ 160 mm Hg[4]	Total cholesterol ≥ threshold[5]	Risk ≥ threshold[6]	Total excluding diabetes	Population in Norway 2015	Numb potent treate
Women											
45 – 54	3529	2.2	4.6	6.2	1.5	1.3	1.4	1.0	16.0	344 481	54 9
55 – 64	2759	4.0	7.2	15.3	4.8	3.5	0.0	1.4	32.2	298 018	96 0
65 – 74	1881	6.0	11.3	25.7	7.7	6.1	0.0	2.4	53.2	241 041	128 1
Men											
45 – 54	2880	3.8	6.7	7.6	2.8	2.7	6.9	11.0	37.8	365 409	138 0
55 – 64	2506	4.9	14.6	15.1	3.5	4.3	5.7	9.6	52.8	305 180	161 1
65 – 74	1885	8.8	24.3	24.5	3.6	4.8	2.7	11.4	71.2	233 524	166 3
											744 665

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 wi underlying genetic lipid disorder. Whereas total cholesterol ≥ 8.0 mmol/l was previously thought to indicate a familial l disorder, today anyone with total cholesterol ≥ 7.0 mmol/l and/or LDL cholesterol ≥ 5.0 mmol/l is highly likely to have disorder. These individuals will have a greater disease risk than their cholesterol level would otherwise suggest because level may have been elevated from a young age. The new guidelines therefore recommend offering statins for primary pr to persons aged < 75 with total cholesterol ≥ 7.0 mmol/l (as opposed to ≥ 8.0 mmol/l previously, provided that LDL cho 5.0 mmol/l), but also to those with LDL cholesterol ≥ 5.0 mmol/l and total cholesterol < 7.0 mmol/l. An important exce women who develop such cholesterol levels *after* the menopause and who have no other risk factors. Reducing the thres ≥ 8.0 mmol/l to ≥ 7.0 mmol/l would, according to similar calculations (Table 4), lead to approximately 25 000 more pe 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 diagno 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. have a good prophylactic effect in the vast majority of patients, and there is insufficient evidence to support the use of sp treatment targets to manage therapy (11). For secondary prevention, LDL cholesterol < 1.8 mmol/l is recommended as a 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 loweri pressure, and the choice of drug will be dictated by additional indications, side effects and contraindications. The new g specify a target blood pressure of <140/90 mm Hg for all patient groups, both in primary and secondary prevention. A s lower treatment target may be considered for patients with diabetes or stroke, while systolic blood pressure of 140 – 150 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-aggre agent), beta-blockers and ACE inhibitors (alternatively angiotensin receptor blockers) in the stable phase following diag coronary artery disease, ischaemic stroke or peripheral atherosclerosis. The recommendations provide general guidelin which drugs to use and for how long, after various types of cardiovascular events. The treatment of hypertension in case 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.

Stain therapy is recommended as secondary prevention for the over 75s as for younger individuals, unless health status expectancy are markedly diminished. Statins should only be used for primary prevention, however, following an individ risk/benefit assessment. Ongoing statin therapy should be discontinued in the event of disease that reduces the expecte 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). Ho treatment of frail elderly patients with markedly reduced life expectancy requires careful consideration, and treatment s 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 a corresponding changes in the recommended intervention thresholds. Changing poor lifestyle habits remains central to c prevention, but whether or not to offer additional pharmacological prevention is an important question that requires ca consideration of the patient's overall situation. The Directorate of Health's guidelines are normative documents, but hea 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 majo progress, remains the most common cause of death in Norway.

LITERATURE

1. Helsedirektoratet. Forebygging av hjerte- og karsykdom. Nasjonal faglig retningslinje for forebygging av hjerteog k https://helsedirektoratet.no/horinger/nasjonal-faglig-retningslinje-for-forebygging-av-hjerte-ogkarsykdom (1.8.201

2. Norheim OF, Gjelsvik B, Kjeldsen SE et al. Retningslinjer for individuell primærforebygging av hjerte- og karsykdo Oslo: Helsedirektoratet, 2009. https://helsedirektoratet.no/retningslinjer/nasjonal-fagligretningslinje-for-individue primerforebygging-av-hjerte-og-karsykdommer (19.6.2017).

3. Selmer R, Lindman AS, Tverdal A et al. Model for estimation of cardiovascular risk in Norway. Tidsskr Nor Laegef 128: 286 - 90 [PubMed].. [PubMed]

4. Norheim OF, Gjelsvik B, Klemsdal TO et al. Norway's new principles for primary prevention of cardiovascular dise differentiated risk thresholds. BMJ 2011; 343: 3626 . [CrossRef].. [CrossRef]

5. Mannsverk J, Wilsgaard T, Mathiesen EB et al. Trends in modifiable risk factors are associated with declining inci hospitalized and nonhospitalized acute coronary heart disease in a population. Circulation 2016; 133: 74 - 81. [PubM [CrossRef]

6. Folkehelserapporten. Hjerte- og karsykdommer i Norge. https://www.fhi.no/nettpub/hin/helse-og-sykdom/hjerte karsykdommer-i-norge---f/ (19.6.2017).

7. Taylor F, Huffman MD, Macedo AF et al. Statins for the primary prevention of cardiovascular disease. Cochrane Da Syst Rev 2013; 31: CD004816 [PubMed].. [PubMed]

8. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of blood pressure reduction in mild hypertens systematic review and meta-analysis. Ann Intern Med 2015; 162: 184 - 91. [PubMed][CrossRef]

9. Nansseu JR, Noubiap JJ. Aspirin for primary prevention of cardiovascular disease. Thromb J 2015; 13: 38. [PubM [CrossRef]

10. National Clinical Guideline Centre (UK). Lipid modification: cardiovascular risk assessment and the modification lipids for the primary and secondary prevention of cardiovascular disease. London: National Institute for Health and Excellence, 2014. https://www.ncbi.nlm.nih.gov/books/NBK248067/ (19.6.2017).

11. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA g on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2014; 63: 2889 - 934. [[CrossRef]

12. Authors/Task Force Members. 2016 European Guidelines on cardiovascular disease prevention in clinical practic Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Preventi Clinical Practice (constituted by representatives of 10 societies and by invited experts)Developed with the special con of the European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016; 37: 2315 - 8 [PubMed][CrossRef]

13. Selmer R, Igland J, Ariansen I et al. NORRISK 2: A Norwegian risk model for acute cerebral stroke and myocardia infarction. Eur J Prev Cardiol 2017; 24: 773 - 82. [PubMed][CrossRef]

14. Naess O, Søgaard AJ, Arnesen E et al. Cohort profile: cohort of Norway (CONOR). Int J Epidemiol 2008; 37: 481 [PubMed][CrossRef]

15. CVDNOR. Cardiovascular Disease in Norway 1994-2014. https://cvdnor.b.uib.no/ (28.1.2017).

16. Helfand M, Buckley DI, Freeman M et al. Emerging risk factors for coronary heart disease: a summary of systema conducted for the U.S. Preventive Services Task Force. Ann Intern Med 2009; 151: 496 - 507. [PubMed][CrossRef]

17. Roksund G, Brodersen J, Johnson GE et al. Overdiagnostikk – norske allmennleger viser vei. Tidsskr Nor Legefor 136: 1903 - 5. [PubMed][CrossRef]

18. Navar-Boggan AM, Peterson ED, D'Agostino RB et al. Using age- and sex-specific risk thresholds to guide statin th one size may not fit all. J Am Coll Cardiol 2015; 65: 1633 - 9. [PubMed][CrossRef]

19. Tromsøundersøkelsen. 2017. Tromsøundersøkelsen. https://uit.no/forskning/forskningsgrupper/gruppe?p_document_id=367276 (19.6.2017).

20. Jenum AK, Graff-Iversen S, Selmer R et al. Risikofaktorer for hjerte- og karsykdom og diabetes gjennom 30 år. Ti Laegeforen 2007; 127: 2532 - 6 [PubMed].. [PubMed]

21. HYVET Study Group. Treatment of hypertension in patients 80 years of age or older. N Engl J Med 2008; 358: 18 [PubMed][CrossRef]

22. Briasoulis A, Agarwal V, Tousoulis D et al. Effects of antihypertensive treatment in patients over 65 years of age: a analysis of randomised controlled studies. Heart 2014; 100: 317 - 23. [PubMed][CrossRef]

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