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İlaç ve Eczacılık Genel Müdürlüğü

ANKARA

Sayı :**B.10.0.İEG.0.13.00.00-610**
Konu :Yazılı Soru Önergesi

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TÜRKİYE BÜYÜK MİLLET MECLİSİ BAŞKANLIĞINA

İlgi :26.06.2006 tarih ve KAN.KAR.MD.A.01.0.GNS.0.10.00.02-22521 sayılı yazıları.

Muğla Milletvekili Sayın Ali ARSLAN tarafından verilen, "Kolesterol ilaçlarında yapılan kısıtlama"ya ilişkin 7/14634 sayılı yazılı soru önergesinin cevabı ilişikte sunulmaktadır.

Arz ederim.

Prof. Dr. Recep AKDAĞ
Sağlık Bakanı

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Muğla Milletvekili Sayın Ali ARSLAN tarafından verilen, "Kolesterol ilaçlarında yapılan kısıtlama"ya ilişkin yazılı soru önergesinin cevabıdır.

SORULAR:

İMF yetkililerin sağlık ve ilaç harcamalarında kısıtlama önerisi Sağlık Bakanlığı tarafından emir kabul edilerek derhal uygulamaya geçilmiştir. Devletin ve Sağlık Bakanlığının öncelikli görevi, halk sağlığını korumak olmasına rağmen gelen talimatla kolesterol hastası kişilerin ilaçlarından kısıtlama yapılarak, hastaların sağlığı tehlikeye atılmıştır.

1-Aldığınız bu kararın tıp bilimine aykırı olduğunun farkında mısınız?

2-İMF nin talimatları mı hastalarımızın ilaç desteğiyle hayatlarını devam ettirmeleri mi önceliklidir?

3-İlaç kullandıkları için kolesterol değerleri normal seviyede olan hastalara yeniden ilaç yazılıncaya kadar geçen sürede ortaya çıkabilecek bir riskin sorumluluğunu kabul ediyor musunuz?

4-Kolesterol hastalarının ilaçlarını keserek ve bu hastaları mağdur ederek sağlık ve ilaç harcamalarını kontrol altında tutabileceğinize inanıyor musunuz?

5-Kolesterol hastalarının ilaçlarını kesmek dışında sağlık ve ilaç harcamalarında tasarruf edebilmek için farklı alternatifler veya İMF' nin dayattığı başka yöntemler var mıdır?

CEVAPLAR:

Kolesterol ilaçları için belirlenen uygulama kriterleri ekte örnekleri sunulan son bilimsel yayınlara uygun olarak hazırlanmış ve insan sağlığı ön planda tutulmuştur.

Kolesterolü yüksek tüm hastaların tedavisindeki ilk basamak diyet ve spordur. Bu tedaviyle yağ düzeyleri istenen seviyeye inmeyen hastalarda ilaç tedavisi başlanmaktadır. "Tedavi Yardımına İlişkin Uygulama Tebliği'nde" (Sıra No: 6) belirtilen ilaca başlama kriterleri son bilimsel kaynak ve referanslara uygundur. Hatta Ülkemizde kullanılan kriterler birçok Avrupa ülkesinden ve Amerika'dan daha fazla erken dönemde hastalara kolesterol ilaçlarının başlanmasına olanak tanımaktadır.

Hastadan istenen tetkik sonuçları ile amaçlanan, hastanın uygun sağlık kuruluşlarında, uygun hekimler tarafından takiplerinin ve kontrollerinin yapılmasıdır. Tetkik ve kontrollerinin sonucuna göre hastaların ilaçla yapılan tedavilerine devam edip etmeyeceklerine karar verilmektedir.Bu konuda kamu tarafından getirilmiş bir kısıtlama söz konusu değildir.

Göstermiş olduğunuz ilgiye teşekkür ederim.

EKLER:
1-The Merck Manual, 8. Baskı (İngilizce) 2006,s.1303-1304
2-NCEP-ATPIII,2001
3-NİCE "Statins for the prevention of cardiovascular events", 2006

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SORULAR:

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4-Kolesterol hastalarının ilaçlarını keserek ve bu hastaları mağdur ederek sağlık ve ilaç harcamalarını kontrol altında tutabileceğinize inanıyor musunuz?

5-Kolesterol hastalarının ilaçlarını kesmek dışında sağlık ve ilaç harcamalarında tasarruf edebilmek için farklı alternatifler veya İMF' nin dayattığı başka yöntemler var mıdır?

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Estimating 10-Year Risk for Men and Women

Risk assessment for determining the 10-year risk for developing CHD is carried out using Framingham risk scoring (Table B1 for men and Table B2 for women). The risk factors included in the Framingham calculation of 10-year risk are: age, total cholesterol, HDL cholesterol, systolic blood pressure, treatment for hypertension, and cigarette smoking. The first step is to calculate the number of points for each risk factor. For initial assessment, values for total cholesterol and HDL cholesterol are required. Because of a larger database, Framingham estimates are more robust for total cholesterol than for LDL cholesterol. Note, however, that the LDL cholesterol level remains the primary target of therapy. Total cholesterol and HDL cholesterol values should be the average of at least two measurements obtained from lipoprotein analysis. The blood pressure value used is that obtained at the time of assessment, regardless of whether the person is on anti-hypertensive therapy. However, if the person is on antihypertensive treatment, an extra point is added beyond points for the blood pressure reading because treated hypertension carries residual risk (see Tables B1 and B2). The average of several blood pressure measurements, as recommended by the Joint National Committee (JNC), is needed for an accurate measure of baseline blood pressure. The designation "smoker" means any cigarette smoking in the past month. The total risk score sums the points for each risk factor. The 10-year risk for myocardial infarction and coronary death (hard CHD) is estimated from total points, and the person is categorized according to absolute 10-year risk as indicated above (see Table 5).

Table B1. Estimate of 10-Year Risk for Men (Framingham Point Scores)

Age	Points
20-34	-9
35-39	-4
40-44	0
45-49	3
50-54	6
55-59	8
60-64	10
65-69	11
70-74	12
75-79	13

Total Cholesterol	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
<160	0	0	0	0	0
160-199	4	3	2	1	0
200-239	7	5	3	1	0
240-279	9	6	4	2	1
≥280	11	8	5	3	1

	Points				
	Age 20-39	Age 40-49	Age 50-59	Age 60-69	Age 70-79
Nonsmoker	0	0	0	0	0
Smoker	8	5	3	1	1

HDL (mg/dL)	Points
≥60	-1
50-59	0
40-49	1
<40	2

Systolic BP (mmHg)	If Untreated	If Treated
<120	0	0
120-129	0	1
130-139	1	2
140-159	1	2
≥160	2	3

Point Total	10-Year Risk %
<0	< 1
0	1
1	1
2	1
3	1
4	1
5	2
6	2
7	3
8	4
9	5
10	6
11	8
12	10
13	12
14	16
15	20
16	25
≥17	≥ 30

NCEP - ATP III

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event in the short term or the long term)—the higher the risk, the lower the goal. Therapeutic lifestyle changes are the foundation of clinical primary prevention. Nonetheless, some persons at higher risk because of high or very high LDL cholesterol levels or because of multiple risk factors are candidates for LDL-lowering drugs. Recent primary prevention trials show that LDL-lowering drugs reduce risk for major coronary events and coronary death even in the short term.

Any person with elevated LDL cholesterol or other form of hyperlipidemia should undergo clinical or laboratory assessment to rule out secondary dyslipidemia before initiation of lipid-lowering therapy. Causes of secondary dyslipidemia include:

- Diabetes
- Hypothyroidism
- Obstructive liver disease
- Chronic renal failure
- Drugs that increase LDL cholesterol and decrease HDL cholesterol (progestins, anabolic steroids, and corticosteroids).

Once secondary causes have been excluded or, if appropriate, treated, the goals for LDL-lowering therapy in primary prevention are established according to a person's risk category (Table 4).

Secondary Prevention With LDL-Lowering Therapy

Recent clinical trials demonstrate that LDL-lowering therapy reduces total mortality, coronary mortality, major coronary events, coronary artery procedures, and stroke in persons with established CHD. As shown in Table 2, an LDL cholesterol level of <100 mg/dL is *optimal;* therefore, ATP III specifies an LDL cholesterol <100 mg/dL as the goal of therapy in secondary prevention. This goal is supported by clinical trials with both clinical and angiographic endpoints and by prospective epidemiological studies. The same goal should apply for persons with CHD risk equivalents. When persons are hospitalized for acute coronary syndromes or coronary procedures, lipid measures should be taken on admission or within 24 hours. These values can guide the physician on initiation of LDL-lowering therapy before or at discharge. Adjustment of therapy may be needed after 12 weeks.

LDL-Lowering Therapy in Three Risk Categories

The two major modalities of LDL-lowering therapy are *therapeutic lifestyle changes* (TLC) and *drug therapy.* Both are described in more detail later. The TLC Diet stresses reductions in saturated fat and cholesterol intakes. When the metabolic syndrome or its associated lipid risk factors (elevated triglyceride or low HDL cholesterol) are present, TLC also stresses weight reduction and increased physical activity. Table 5 defines LDL cholesterol goals and cutpoints for initiation of TLC and for drug consideration for persons with three categories of risk: CHD and CHD risk equivalents; multiple (2+) risk factors (10-year risk 10-20% and <10%); and 0-1 risk factor.

Table 5: LDL Cholesterol Goals and Cutpoints for Therapeutic Lifestyle Changes (TLC) and Drug Therapy in Different Risk Categories.

Risk Category	LDL Goal	LDL Level at Which to Initiate Therapeutic Lifestyle Changes (TLC)	LDL Level at Which to Consider Drug Therapy
CHD or CHD Risk Equivalents (10-year risk >20%)	<100 mg/dL	≥100 mg/dL	≥130 mg/dL (100-129 mg/dL: drug optional)*
2+ Risk Factors (10-year risk ≤20%)	<130 mg/dL	≥130 mg/dL	10-year risk 10-20%: ≥130 mg/dL 10-year risk <10%: ≥160 mg/dL
0-1 Risk Factor†	<160 mg/dL	≥160 mg/dL	≥190 mg/dL (160-189 mg/dL: LDL-lowering drug optional)

* *Some authorities recommend use of LDL-lowering drugs in this category if an LDL cholesterol <100 mg/dL cannot be achieved by therapeutic lifestyle changes. Others prefer use of drugs that primarily modify triglycerides and HDL, e.g., nicotinic acid or fibrate. Clinical judgment also may call for deferring drug therapy in this subcategory.*

† *Almost all people with 0-1 risk factor have a 10-year risk <10%, thus 10-year risk assessment in people with 0-1 risk factor is not necessary.*

CHD and CHD risk equivalents

For persons with CHD and CHD risk equivalents, LDL-lowering therapy greatly reduces risk for major coronary events and stroke and yields highly favorable cost-effectiveness ratios. The cut-points for initiating lifestyle and drug therapies are shown in Table 5.

- *If baseline LDL cholesterol is ≥130 mg/dL,* intensive lifestyle therapy and maximal control of other risk factors should be started. Moreover, for most patients, an LDL-lowering drug will be required to achieve an LDL cholesterol <100 mg/dL; thus an LDL cholesterol lowering drug can be started simultaneously with TLC to attain the goal of therapy.

If LDL cholesterol levels are 100-129 mg/dL, either at baseline or on LDL-lowering therapy, several therapeutic approaches are available:

TABLE 159–5. NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL III GUIDELINES FOR TREATMENT OF HYPERLIPIDEMI

RISK CATEGORY	BEGIN LIFESTYLE CHANGES IF:	CONSIDER DRUG THERAPY IF:	LDL G
High: CAD or CAD equivalents (10-yr risk > 20%)	LDL ≥ 100 mg/dL (2.58 mmol/L)	LDL ≥ 100 mg/dL (2.58 mmol/L)(drug optional if < 100 mg/dL [< 2.58 mmol/L])	< 100 mg/ <70 m optiona
Moderate high: ≥ 2 risk factors with 10-yr risk 10 to 20%*	LDL ≥ 130 mg/dL (3.36 mmol/L)	LDL ≥ 130 mg/dL (3.36 mmol/L)	<130 mg/ <100 m optiona
Moderate: ≥ 2 risk factors with 10-yr risk < 10%*	LDL ≥ 130 mg/dL (3.36 mmol/L)	LDL ≥ 160 mg/dL (4.13 mmol/L)	<130 mg/ <100 m optiona
Lower: 0–1 risk factor	LDL ≥ 160 mg/dL (4.13 mmol/L)	LDL ≥ 190 mg/dL (4.91 mmol/L) (drug optional if 160–189 mg/dL [4.13–4.88 mmol/L])	<160 mg/

*For 10-yr risk, see Framingham risk tables (TABLES 159–6 and 159–7).

CAD = coronary artery disease; LDL = low-density lipoprotein.

Data from the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of Blood Cholesterol in Adults. National Institutes of Health, National Heart, Lung, and Blood Insti 2001 and from Grundy SM, Cleeman JI, Merz CNB, et al. Implications of recent clinical trials fo National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulat* 2004;110:227–239.

mg/dL [>5.2 mmol/L]) and those at high cardiovascular risk, drug therapy should accompany diet and exercise from the start.

Statins are the drugs and possibly treatment of choice for LDL reduction and demonstrably reduce cardiovascular mortality. Statins inhibit hydroxymethylglutaryl CoA reductase, a key enzyme in cholesterol synthesis, leading to up-regulation of LDL receptors and increased LDL clearance. They reduce LDL by up to 60% and produce small increases in HDL and modest decreases in TGs. Statins also appear to decrease intra-arterial and/or systemic inflammation by stimulating production of endothelial nitric oxide; they may also decrease LDL deposition in endothelial macrophages and decrease cholesterol in inflammatory cell membranes. This anti-inflammatory effect is antiatherogenic even in the absence of elevated lipid levels. Adverse effects are uncommon but include liver enzyme elevations and myositis or rhabdomyolysis. Muscle toxicity without enzyme elevation has also been reported. Adverse effects are more common in older patients, those with multiple diseases, and those on multiple drugs. In some pe changing from one statin to another o ering the dose relieves the problem. M toxicity seems to be most common w some of the statins are used with drugs tha hibit cytochrome P3A4 (eg, macrolide biotics, azole antifungals, cyclosporine with fibrates, especially gemfibrozil. Pro ties of statins differ slightly by agent, and choice of agent should be based on pa characteristics, LDL level, and provide cretion (see TABLE 159–8).

Bile acid sequestrants block intestinal acid reabsorption, forcing up-regulation hepatic LDL receptors to recruit circul cholesterol for bile synthesis. They proven to reduce cardiovascular mort Bile acid sequestrants are usually used statins or with nicotinic acid (see p. 1308 augment LDL reduction and are the dru choice for children and women who are planning to become pregnant. Bile ac questrants are safe, but their use is limit adverse effects of bloating, nausea, cra ing, and constipation. They may also incr TGs, so their use is contraindicated in pa

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hypertriglyceridemia. Cholestyramine olestipol, but not colesevelam, interfere absorption of other drugs—notably thi- β-blockers, warfarin, digoxin, and oxine—an effect that can be minimized dministration 4 h before or 1 h after other

zetimibe inhibits intestinal absorption of olesterol and phytosterol. It usually lowers DL by 15 to 20% and causes small increases HDL and a mild decrease in TGs. Ezetimibe be used as monotherapy in patients intol- nt to statins or added to statins for patients aximum doses with persistent LDL ele- ion. Adverse effects are infrequent.

Dietary supplements that lower LDL lev- include fiber supplements and commer- lly available margarines containing plant sterols (sitosterol and campesterol) or stanols. The latter reduce LDL by up to 10% without affecting HDL or TGs by competitively displacing cholesterol from intestinal micelles. Garlic supplements and walnuts have been advocated for LDL reduction with only minimal evidence to support their use.

Procedural approaches are reserved for patients with severe hyperlipidemia (LDL > 300 mg/dL) that is refractory to conventional therapy, such as occurs with familial hypercholesterolemia. Options include LDL apheresis (in which LDL is removed by extracorporeal plasma exchange), ileal bypass (to block reabsorption of bile acids), liver transplantation (which transplants LDL receptors), and portocaval shunting (which decreases LDL production by unknown mechanisms).

TABLE 159–6. FRAMINGHAM RISK TABLES FOR MEN

	POINT SCORE									
AGE	20–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75–79
points	–9	–4	0	3	6	8	10	11	12	13
<160	0	0	0	0	0	0	0	0	0	0
60–199	4	4	3	3	2	2	1	1	0	0
200–239	7	7	5	5	3	3	1	1	0	0
240–279	9	9	6	6	4	4	2	2	1	1
≥280	11	11	8	8	5	5	3	3	1	1
onsmoker	0	0	0	0	0	0	0	0	0	0
moker	8	8	5	5	3	3	1	1	1	1
DL ≥60	–1									
50–59	0									
40–49	1									
<40	2									
stolic BP <120	Untreated 0; treated 0									
120–129	Untreated 0; treated 1									
130–139	Untreated 1; treated 2									
140–159	Untreated 1; treated 2									
≥160	Untreated 2; treated 3									

POINTS (10-yr risk of MI or CAD death %): < 0 points = < 1%; 0–4 points = 1%; 5–6 points = points = 3%; 8 points = 4%; 9 points = 5%; 10 points = 6%; 11 points = 8%; 12 points = 10%; points = 12%; 14 points = 16%; 15 points = 20%; 16 points = 25%; >17 points = ≥30%.

=total cholesterol; HDL = high-density lipoprotein; CAD = coronary artery disease.

ata from the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High lood Cholesterol in Adults. National Institutes of Health, National Heart, Lung, and Blood Institute,

protein and homocysteine measurement may be considered in the same populations.

Tests for secondary causes of dyslipidemia—including measurements of fasting glucose, liver enzymes, creatinine, thyroid stimulating hormone (TSH), and urinary protein—should be performed in most patients with newly diagnosed dyslipidemia, and when a component of the lipid profile has inexplicably changed for the worse.

Prognosis and Treatment

Prognosis varies with lipid levels and other cardiovascular risk factors.

General principles: Treatment is indicated for all patients with cardiovascular disease (secondary prevention) and for some without (primary prevention). The National Institutes of Health's National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines are the most common reference for deciding which adults should be treated (see TABLES 159–4 and 159–5). The guidelines focus primarily on reducing elevated LDL levels and secondarily on treating high TGs, low HDL, and metabolic syndrome (see p. 61). An alternate treatment guide (the Sheffield table) uses TC:HDL ratios combined with presence of CAD risk factors to predict cardiovascular risk, but this approach probably leads to undertreatment.

Treatment of children is controversial; dietary changes may be difficult to implement, and no data suggest that lowering lipid levels in childhood effectively prevents heart disease in adulthood. Moreover, the safety and effectiveness of long-term lipid-lowering treatment are questionable. Nevertheless, the American Academy of Pediatrics (AAP) recommends treatment for some children who have elevated LDL levels.

Treatment options depend on the specific lipid abnormality, although different lipid abnormalities often coexist. In some patients, a single abnormality may require several therapies; in others, a single treatment may be adequate for several abnormalities. Treatment should always include treatment of hypertension and diabetes, smoking cessation, and in those with a 10-yr risk of MI or death from CAD of ≥ 10% (as determined from the Framingham tables—see TABLES 159–6 and 159–7), low-dose daily aspirin. In general, treatment options for men and women are the same.

Elevated LDLs: ATPIII guidelines recommend treatment for adults with elevated LDL levels and a history of CAD; conditions that confer a risk for future cardiac events similar to that of CAD itself (CAD equivalents, defined as diabetes mellitus, abdominal aortic aneurysm, peripheral arterial disease, and symptomatic carotid artery disease); or ≥ 2 CAD risk factors. ATPIII guidelines recommend that these patients have LDL levels lowered to < 100 mg/dL, but accumulating evidence suggests that this target may be too high and a target LDL < 70 mg/dL is an option for patients at very high risk (eg, those with known CAD and diabetes, other poorly controlled risk factors, metabolic syndrome, or acute coronary syndrome). When drugs are used, a dose providing at least a 30 to 40% decrease in LDL is desirable (see TABLE 159–8).

The AAP recommends dietary treatment for children with LDL > 110 mg/dL. Drug therapy is recommended for children > 10 yr who are poorly responsive to dietary therapy and who have LDLs ≥ 190 mg/dL without a family history of premature cardiovascular disease. Drug therapy is also recommended for children > 10 yr with LDLs ≥ 160 mg/dL and a family history of premature cardiovascular disease or ≥ 2 risk factors for premature cardiovascular disease. Childhood risk factors besides family history and diabetes include cigarette smoking, hypertension, low HDLs (< 35 mg/dL), obesity, and physical inactivity.

Treatment options include lifestyle changes (diet and exercise), drugs, dietary supplements, procedural interventions, and experimental therapies. Many of these are also effective for treating other lipid abnormalities. Exercise directly lowers LDL in some people; it is also essential to maintain ideal body weight. Dietary changes and exercise should be the initial approach whenever feasible.

Dietary changes include decreasing intake of saturated fats and cholesterol; increasing intake of monounsaturated fats, dietary fiber, and complex carbohydrates; and maintaining ideal body weight. Referral to a dietitian is often useful, especially for older people.

The length of time for which lifestyle changes should be attempted before beginning lipid-lowering drugs is controversial. In patients at average or low cardiovascular risk, 3 to 6 mo is reasonable. Generally, 2 to 3 visits with a patient over 2 to 3 mo are sufficient to assess motivation and adherence.

Drugs are the next step when lifestyle changes are not effective. However, for patients with extremely elevated LDLs (≥ 20

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TABLE 159–4. NATIONAL CHOLESTEROL EDUCATION PROGRAM ADULT TREATMENT PANEL III APPROACH TO DYSLIPIDEMIAS

Measure fasting lipoproteins (in mg/dL):

TC (mmol/L)	
< 200 (5.17)	Desirable
200–239 (5.17–6.18)	Borderline high
≥ 240 (6.20)	High
LDL	
< 100 (2.58)	Optimal
100–129 (2.58–3.33)	Near optimal/above optimal
130–159 (3.36–4.11)	Borderline high
160–189 (4.13–4.88)	High
≥ 190 (4.91)	Very high
HDL	
< 40 (1.03)	Low
≥ 60 (1.55)	High
TG	
< 150	Desirable
150–199 (1.695–2.249)	Borderline high
200–499 (2.26–5.639)	High
≥ 500 (5.65)	Very high

Identify CAD or CAD equivalents (if present, see TABLE 159–5)

CAD equivalents
- Other atherosclerotic disease:
  - Peripheral arterial disease
  - Abdominal aortic aneurysm
  - Symptomatic carotid artery disease
- Diabetes mellitus
- Additional risk factors that confer 10-yr risk of MI or CAD death > 20% (see TABLES 159–6 and 159–7)

Identify major CAD risk factors
- Cigarette smoking
- Hypertension (BP ≥ 140/90 *or* on antihypertensive drug)
- Low HDL (≤ 40 mg/dL [1.03 mmol/L])
- Family history of premature CAD (CAD in male 1st-degree relative < 55 or in female 1st-degree relative < 65)
- Age (men ≥ 45, women ≥ 55)

If ≥ 2 major risk factors are present without CAD or CAD equivalent, assess 10-yr risk of MI or CAD death using Framingham risk tables (see TABLES 159–6 and 159–7).

TC = total cholesterol; LDL = low-density lipoprotein; HDL = high-density lipoprotein; TG = triglyceride; CAD = coronary artery disease.

Data from the Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Institutes of Health, National Heart, Lung, and Blood Institute,

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currently under development. It was aware that this clinical guideline would also consider the use of cholesterol target levels and the associated pathways of care for people with dyslipidaemia.

4.3.6 The Committee discussed in detail the results of the economic analyses from the manufacturers' models and the Assessment Group's model. It concluded that the Assessment Group's model, which estimated cost effectiveness for statins as a class, represented the most appropriate analysis on which to base its decision regarding the initiation of statin treatment. This was because the model used clinical events to measure effectiveness rather than the surrogate endpoint of cholesterol lowering, and it presented health outcomes in terms of QALYs. The Committee noted that this analysis excluded evidence on rosuvastatin because data on clinical events were not available. Of the three scenarios presented as part of the Assessment Group's model (see Section 4.2.11), the Committee agreed that Scenario 2, the analysis of people at risk of CVD, taking into account CVD outcomes, was the most appropriate. It noted that the sensitivity analyses related to the base case analysis (see Section 4.2.11) but concluded that the same general patterns of uncertainty would also apply to Scenario 2.

4.3.7 The Committee acknowledged the uncertainties around the results of the Assessment Group's primary prevention model. It was aware of substantial recent reductions in the prices of some statins, in particular simvastatin and pravastatin, and noted that this would significantly reduce the incremental costs per QALY estimated by the Assessment Group. The Committee considered that a time horizon based on the costs and health outcomes associated with a lifetime of statin therapy was the most appropriate for the economic analysis, given that statin therapy is a lifelong treatment and benefits occur well into the future. It acknowledged, however, that this extrapolation of the available data introduced additional uncertainty into the results, and that shortening the time horizon, to 20 years or less, markedly increased the incremental costs per QALY estimates. The Committee also noted the marked effect that discount rates had on the results, and that

applying rates of 3.5% to both costs and QALYs (instead of 6% for costs and 1.5% for QALYs) substantially increased the incremental costs per QALY. It accepted that the discount rates for this appraisal require the use of 6% for costs and 1.5% for QALYs, but it considered that the alternative rates were important for a check on the sensitivity of the results to change.

4.3.8 The Committee also carefully considered the Assessment Group's re-analysis of the cost effectiveness of statin therapy on the basis of decreasing risk in a stepwise manner (for example, from a threshold of 3% annual risk to 2% annual risk – see Section 4.2.27). It concluded that, although this analysis related to Scenario 1 of the Assessment Group's model (see Section 4.2.11), it gave an important insight into the true incremental cost effectiveness of treating decreasing levels of absolute risk and usefully supplemented the analysis based upon individual single point estimates of risk.

4.3.9 The Committee considered the nature of the population who would be treated with statins for primary prevention. It acknowledged that this group was essentially asymptomatic or free of CVD but at measurable risk of future events. The Committee noted that the Assessment Group's additional analysis suggested that it might be cost effective to initiate statin therapy in people with an annual risk of a CHD event lower than 1.5% (approximately equivalent to a 10-year risk of a CVD event lower than 20%). However, it was concerned by the uncertainty associated with the cost-effectiveness results, particularly at lower levels of CVD risk, because most of the clinical trials included in the review did not include people at very low risk of a CHD event. Additionally, the Committee took into consideration the risks of adverse events associated with the use of statins and that these should be taken into account when initiating lifelong treatment in a large population at a low risk of CVD. The Committee was also aware of the possibility that further adverse events might become apparent with extended use in wider populations and over time. Taking account of these factors and those outlined in Section 4.3.7, and the need to consider the effective use of NHS

resources given the large eligible population, the Committee concluded that initiation of statin therapy for primary prevention would be most appropriate in people at a 20% or greater 10-year CVD risk.

4.3.10 The Committee noted the increase in the incremental costs per QALY at all levels of risk in people over the age of 75 years in the economic model. It acknowledged that this change reflected the fact that older people have a higher risk of death from other causes, a higher prevalence of comorbidities and a shorter life expectancy, and hence have a lower capacity to benefit overall from statin therapy. However, taking into consideration the recent reductions in the prices of some statins, the Committee noted that statin therapy would be cost effective for all age groups at a 20% or greater 10-year risk of CVD. It was also aware that current risk calculators are not validated for individuals over the age of 70 years, and concluded that CVD risk should be estimated on the basis of a clinical assessment.

4.3.11 Consideration was given to the use of statins in people with diabetes. The Committee accepted that generally people with diabetes have a higher absolute risk of CVD compared with people without diabetes. It was aware that the review of clinical and cost effectiveness included evidence relating to the use of statins in type 2 diabetes only, and that statin therapy was cost effective in this group of people. The Committee was also aware that the absolute risk of CVD in people with diabetes varied according to the type of diabetes (type 1 or type 2) present. The Committee further noted the limitations of assessing risk in people with diabetes using standard risk calculators. The Committee concluded that the decision whether to initiate statin therapy in people with diabetes should be made where a clinical assessment has estimated the CVD risk to be likely to be equivalent to at least 20% over 10 years.

4.3.12 The Committee was also aware that people from some ethnic groups have a particularly high prevalence of CVD, although there are no validated risk assessment tools for such groups. The Committee agreed that the decision whether to initiate statin therapy in such groups should therefore be made where a clinical assessment has estimated the CVD risk to be likely to be equivalent to at least 20% over 10 years.

4.3.13 The Committee was mindful that the initiation of statin therapy may not be an appropriate recommendation in all people. It considered that, when initiating statin therapy, clinicians should take into account all factors that relate to the individual's life expectancy and capacity to benefit from the reduction in cardiovascular events associated with statin usage. The Committee concluded that the decision whether to initiate statin therapy in any one individual, regardless of age, should be made after informed discussion between the responsible clinician and the patient about the risks and benefits of statin treatment and taking into account factors such as comorbidities and life expectancy.

4.3.14 The Committee noted from the evidence available that, for the purposes of initiating therapy, there were no data on clinical events to suggest the superiority of any one statin over all the others in reducing cardiovascular events. It was mindful that data on clinical events were not currently available for rosuvastatin. It was also aware of the substantial differences in price between the different statins, resulting partly from the recent large reductions in the price of some statins, and of the potential for future price changes. The Committee concluded that, when the decision has been made to initiate a statin, therapy should usually be initiated with a drug with a low acquisition cost (taking into account required daily dose and product price per dose).

4.3.15 Finally, the Committee discussed the importance of other strategies for managing CVD risk over and above statin therapy, such as lifestyle measures and other drug therapies. It concluded that, although making recommendations on other management strategies was outside the remit of the current appraisal, the guidance should be issued on the assumption that