Tidsskriftet Tidsskrift for Den norske legeforening

Cardiovascular disease and diabetes in patients with African or Asian background

REVIEW ARTICLE

ARILD AAMBØ

E-mail: a.aa@nakmi.no
Norwegian Centre for Migration and Minority Health (NAKMI)
Oslo University Hospital, Aker
He is the author of this article.
Arild Aambø (born 1949), doctor and former specialist in primary care medicine. He is a senior adviser at NAKMI and has been a member of the Norwegian Directorate of Health's expert group for the prevention of diabetes-related macrovascular complications.
The author has completed the ICMJE form and reports no conflicts of interest.

TOR OLE KLEMSDAL

Preventive cardiology
Oslo University Hospital, Aker
He has contributed with thorough discussions on the topic, design and revision of the manuscript, reading and commentary, and has approved the submitted version of the manuscript.
Tor Ole Klemsdal (born 1958), specialist in internal medicine and cardiology, senior consultant and head of department. He has been a member of the Norwegian Directorate of Health's expert group for the prevention of diabetes-related macrovascular complications and has been commissioned by the Directorate of Health in a 20 % FTE position for work on these and other guidelines.
The author has completed the ICMJE form and reports the following conflicts of interest: He has received lecture fees from MSD Norge, Astra Zeneca, BMS-Squibb Norway, Novartis Norge and Sanofi-Aventis Norge.

BACKGROUND

Population groups of different ancestry appear to have varying prevalence of diabetes, different risks of developing cardiovascular disease and different responses to certain drugs that are used for these conditions. We wished to review the literature in this field.

MATERIAL AND METHOD

We have performed searches in several databases for systematic review articles published from the year 2000 onwards, and supplemented these with articles from reference lists, our own literature archives and a pyramid search in the Norwegian Electronic Health Library database. Altogether 37 articles were included.

RESULTS

With regard to diagnosed diabetes, the prevalence of coronary heart disease and stroke varies among groups of South Asian, East Asian, African and European ancestry. In patients of South Asian ancestry, the risk of coronary heart disease appears to be twice that of Europeans, and the disease occurs 5–10 years earlier. The prevalence of stroke is especially high in persons of African ancestry. Risk factors such as dyslipidemia and hypertension are distributed differently among these groups. The therapeutic response to drugs such as beta blockers, ACE inhibitors and various statins differs; for example, statin doses in Asians may often be halved in relation to those used for Caucasians, and ACE inhibitors are not recommended as monotherapy for hypertension in persons of African ancestry. These differences are partly attributable to variations in genetic disposition.

INTERPRETATION

The findings are clinically significant – better insight in this field enables optimal tailoring of treatment for each patient, with more rapid achievement of goals and reduced risk of adverse effects. The recommendations given in this article are consistent with and complement the Directorate of Health's revised guidelines for the treatment of diabetes.

In a culturally complex society such as that of Norway, the requirement for equal treatment irrespective of age, sex and ancestry is particularly important, as significant differences have been detected between various ethnic groups with regard to both disease prevalence and response to drug therapy (1). The proportion of patients in one particular population group who respond positively to a drug may differ from the proportion who respond positively in another group. This variation in drug response is to some extent genetically determined (1).

It is therefore conceivable that these characteristics apply not only to particular ethnic groups in their respective areas and countries of ancestry; they are also widespread in those who emigrate. This is true even though the prevalence of diabetes and macrovascular disease is affected to a large degree by lifestyle, living conditions and other factors that are brought about by migration (2–4). It is also well known that dietary ingredients can influence the efficacy of certain drugs (5).

Due to the complexity of the relationship between diabetes, macrovascular disease, genetic factors, diet and lifestyle (2), in this article we have chosen to take a pragmatic approach.

We wished to elucidate whether the prevalence of cardiovascular disease, hypertension and/or hyperlipidemia differs in diabetes patients of African or Asian ancestry compared to Caucasians. We also wished to discover whether diabetes patients of African or Asian ancestry respond differently from Caucasians to drugs for the prevention of cardiovascular disease.

Material and method

In the spring of 2015, a literature search was undertaken in connection with preparatory work for the Directorate of Health's new guidelines for the treatment of diabetes (6) and in collaboration with the Directorate of Health's library service. We wished to concentrate our search on studies that were conducted among migrants to Europe, but also wished to include studies from the country of ancestry or the region from which the migrants came, as we believe that this can help to increase understanding.

We searched in the databases PubMed, Ovid MEDLINE, EMBASE, Global health, Cochrane Database of Systematic Reviews, NHS Economic Evaluation Database, Other Reviews (DARE), Technology Assessment, EBSCOs Cinahl, CDSR, EED, and SveMed+ for systematic reviews in Norwegian, Swedish, Danish, English and German, published from and including the year 2000.

In order to address the first research question, we used the following search string (simplified): Diabetes mellitus AND Asia OR Africa AND Hypertension OR Myocardial infarction OR Stroke. The search was concluded on 4 February 2015.

In order to shed light on the second research question, we used the following search string (simplified): Diabetes AND Asia OR Africa AND Statin* OR Antihypertensive* OR Thiazide* OR Diuretic*. To ensure that we included literature relevant to the key groups that have come from Asia and Africa to Norway, we also conducted a search on a discretionary selection of national groups from these regions. This search was concluded on 30 March 2015. The full search strategy can be found in Aambø's appendix.

We obtained a total of 871 hits, and having removed any duplicates 787 hits remained. The relevance of the articles was initially assessed by the first author based on the title and abstract (Figure 1). A total of 34 articles were read in full text. Of these, we found five review articles from the period 2005–15. The material was further supplemented with three more recent review articles first published in the period 2015–16 (7–9).

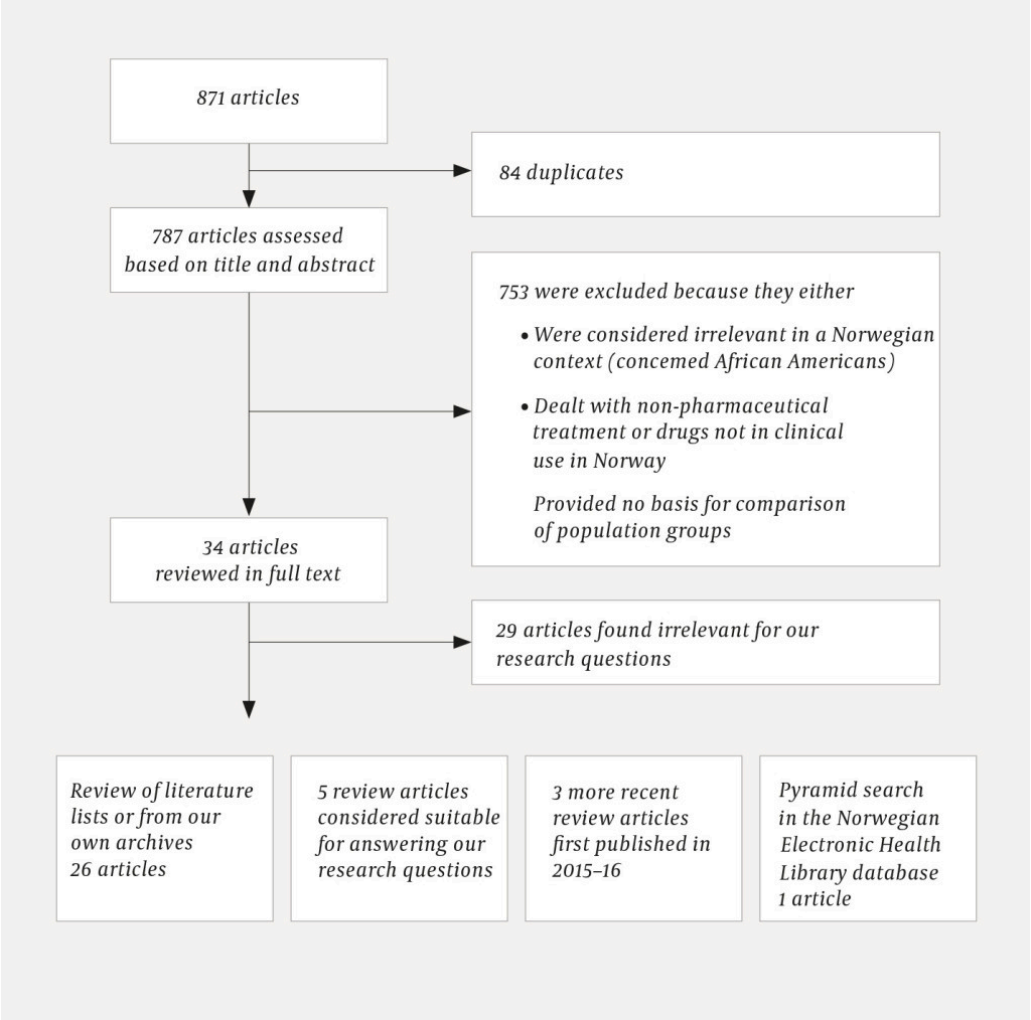

Figure 1 Result of searches for articles from the period 2000–15

Based on findings in the selected articles, in March 2015 three pyramid searches were also performed in the Norwegian Electronic Health Library database, for 'hypertension AND pharmacogenomics', '825T AND hypertension' and 'CYP2C19 AND Asian OR African', respectively. One article was included from these searches (10). A further 26 articles were included after reviewing the reference lists of the selected articles, as well as articles from our own archives (11–38).

In this article, we use 'ancestry' to denote the population in the country of origin, migrants from this region and their descendants.

Prevalence

Significant variation exists between different ethnic groups with respect to the prevalence of diabetes and cardiovascular diseases (11, 12), and this variation is reflected in immigrants from the respective regions. Although we wished to investigate the risk of diabetes-related cardiovascular disease in different population groups, in practice it is difficult to distinguish clearly between risk of diabetes, risk of cardiovascular disease and risk of both, as several risk factors are common to both and the diseases often develop over time.

Insulin resistance, for example, is more frequent among the ethnic groups concerned, which predisposes them to the development of both diabetes and cardiovascular disease, and not necessarily via diabetes (39, 40). Nor do the respective authors operate with such clear divisions in our evidence base.

For persons of South Asian ancestry, the probability of developing coronary heart disease is estimated to be 1.5 times higher than in Europeans, and five times higher than in the Chinese. Moreover, the disease occurs on average 5–10 years earlier (7, 13, 14, 41). Among South Asians, insulin resistance probably has more bearing on the development of diabetes than loss of beta-cell function (15).

This group also presents a unique lipid profile – with high triglyceride and lipoprotein levels (a) combined with low levels of HDL cholesterol. The HDL cholesterol particles also tend to be smaller and are more often dysfunctional. Moreover, there is an increased prevalence of highly atherogenic, small dense LDL particles, even though the total LDL level is on a par with that of other population groups (8, 9, 16). It also appears that hyperglycaemia has a greater impact on left ventricular function in South Asians than in Caucasians, which often manifests itself as fatigue and reduced capacity for work (17, 18).

Among immigrants to Europe of African ancestry, hypertension occurs up to 3–4 times as frequently as in the general population (19, 42). The condition is more often characterised by a low renin level, and hypertension appears at a younger age, the rise in blood pressure is higher and nocturnal fall in blood pressure is less. This represents an increased risk of stroke, left ventricular hypertrophy and renal injury (42). However, the lipid profile in this group appears to be favourable; they have a higher HDL cholesterol level and lower levels of triglycerides and total cholesterol than the general population (42).

Response to prophylactic drugs

Antihypertensives

In diabetes patients of East Asian ancestry, beta blockers (propranolol) appear to reduce blood pressure and heart rate *more* effectively than in Caucasians. They respond to lower doses, but metabolise and excrete the drug more rapidly (1, 24).

A meta-analysis on the efficacy of antihypertensive monotherapy in diabetes patients of African ancestry (20) shows that:

- beta blockers provide minimal reduction in systolic blood pressure, and difference from placebo is uncertain
- calcium channel blockers and thiazides both effectively lower blood pressure
- ACE inhibitors have little effect on diastolic blood pressure, but appear to reduce the risk of renal injury

ACE inhibitors reduced blood pressure to a lesser extent in persons of African ancestry than in Caucasians – the average difference was 4.6 mm Hg in systolic and 2.8 mm Hg in diastolic pressure (21). ACE inhibitors should therefore not be the first-line drugs in cases of uncomplicated, mild or moderate hypertension in this group (21, 24).

These findings point to a genetic predisposition. The prevalence of a genetic variant, *GNB3* C825T (22), varies strongly between different nationalities and ethnic groups: In Ghana it is 91 %, in Kenya 89 %, among East Asians 50 % and among Germans and Spaniards 30 % (23). However, the clinical significance of this is still unclear (10).

East Asians have an approximately threefold greater risk of cough with the use of ACE inhibitors (24). Individuals of African origin have a threefold greater risk of developing angioedema with ACE inhibitors and a significantly increased tendency to develop depression with the use of thiazides (24).

If beta blockers are indicated for East Asians (for example in cases of arrhythmia, angina pectoris or heart failure), doctors should be aware that despite more rapid drug metabolism, the clinical effect of some beta blockers may be more pronounced than in Caucasians (1, 24).

Monotherapy for hypertension is not recommended for diabetes patients of African ancestry, but rather a combination of a calcium antagonist and ACE inhibitor (18, 25, 26). ACE inhibitors are preferred to thiazides because they work well in combination with other drugs, and moreover reduce the risk of renal injury. If this is insufficient, a thiazide may be added. A fourth drug may in some cases also be appropriate (26).

Lipid-lowering agents

Studies of statin use in different population groups reveal that East Asians achieve the same response as persons of different ancestry at significantly lower doses. For patients in Japan, a dose of 5 mg simvastatin was equally effective on LDL cholesterol level as a dose of 20 mg, which is used in Western countries (27). Treatment with 10 mg atorvastatin or 10 mg simvastatin lowered the LDL cholesterol level in Asians over the course of eight weeks by 43 % and 35 % respectively, and more than 80 % of the patients achieved their treatment goals at these doses (27).

Furthermore, diabetes patients of South Asian ancestry respond well to both rosuvastatin and atorvastatin, and in one study 70–90 % achieved their treatment goal (in this case set at < 2.6 mmol/l) with doses of 10–20 mg (28).

Among African Americans, rosuvastatin (10 mg and 20 mg) resulted in a significantly greater improvement in the lipid profile than similar doses of atorvastatin (29). The different effects of statins may be attributable to variations in pharmacokinetic response, which is usually genetically determined. One study showed, for example, that 40 mg rosuvastatin resulted in a maximum plasma concentration that was 2.4 times higher in Chinese, 2.0 times higher in Malaysians and 1.7 times higher in Indians than in Caucasians (30).

Myalgia, the most common adverse effect of statins, is dose-dependent and estimated to occur in 10–15 % of users (31, 32). It may appear that persons of Asian and African ancestry are particularly vulnerable (33). There is a possible relationship between vitamin D deficiency and statin-induced myalgia (34). It is important to be aware of this with regard to certain groups of immigrants whose level of vitamin D may be very low (35). After a treatment break during which the vitamin D level is normalised, the treatment can in many cases be resumed without the pain recurring (34, 36).

The interaction between statins and CYP3A4 inhibitors (e.g. calcium channel blockers), which are recommended for hypertension in persons of African ancestry (20), can also result in myalgia (37).

The clinical significance of these adverse effects should not be underestimated. Even mild adverse effects may lead patients to discontinue their medicine.

If no macrovascular disorder is present, the recommendation is that South Asians, like others with diagnosed diabetes, should receive statins (6), but generally at lower doses (27). When it comes to drugs for which the recommended doses for Caucasians are 10–40 mg per day, Asians should take 5–20 mg (27). Moreover, the treatment should be started before the age of 40, i.e. before the age that is generally recommended in Norway (6). Some doctors suggest a treatment goal of less than 70 mg/100 ml for the LDL cholesterol level, or approximately 1.8 mmol/l, for this group (38), while a treatment goal of < 2.5 mmol/l is generally applied in the primary prevention of diabetes (6).

Discussion

This literature review reveals significant differences between population groups of different ancestry with regard to prevalence of diabetes complications, drug response and adverse effects. However, our evidence base has several weaknesses, and we are therefore currently unable to make firm recommendations based on ancestry.

Firstly, it is not always clear which national groups are included under collective terms such as 'Asians' and 'Africans' or subgroups such as 'South Asians' or 'East Asians'. Secondly, wide variation exists *within* these groups, not least in terms of genetic factors. Genetic disposition is also difficult to distinguish from living conditions, lifestyle and other factors that to a large extent are brought about by migration. Equality of treatment must therefore be assessed based on the effect achieved, viewed in relation to possible adverse effects in each individual patient (1).

However, clinicians should be aware that in the prevention and/or treatment of diabetes in patients of Asian or African ancestry, they may encounter more cases of 'non-responders' (patients for whom the drug is ineffective, but adverse effects may occur despite this), as well as more frequent adverse effects, such as myalgia, with the use of statins (33).

There is also apparent agreement that diabetes patients of African ancestry with hypertension should not receive monotherapy with ACE inhibitors, but combination treatment with ACE inhibitors and calcium channel blockers, or ACE inhibitors and a thiazide (25, 26). In persons of South Asian ancestry with diabetes, primary prevention with statins should be considered earlier than the general recommendation states (i.e. before that age of 40) and at somewhat lower LDL cholesterol values (6, 38).

As a general rule, we say 'start lower, go slower', i.e. start with relatively low doses, increase with caution until the desired effect is achieved, and pay particular attention to adverse effects. In the absence of any effect, switching to a different drug should be considered at an early stage.

Finally, we would like to remind doctors that patients may have particular challenges related to language, prior knowledge and possibly understanding of their illness. This requires good communication skills and ample time to ensure that patients understand that prophylactic treatment is not a 'cure', but a measure that requires permanent medication (43, 44).

We would like to thank Marianne Kringen and Espen Molden, the Center for Psychopharmacology, Diakonhjemmet Hospital, and John Cooper, Stavanger University Hospital, for their useful comments on an earlier draft of this article

Main message

There are significant differences in the prevalence of diabetes-related macrovascular disease between persons of African, Asian and European ancestry

In persons of African and Asian ancestry, drug treatment should be initiated with somewhat lower doses and carefully increased until the desired effect is achieved

Persons of African ancestry with hypertension should receive combination treatment, either with ACE inhibitors and calcium channel blockers or with ACE inhibitors and a thiazide drug

LITERATURE

1. Burroughs VJ, Maxey RW, Levy RA. Racial and ethnic differences in response to medicines: towards individualized pharmaceutical treatment. J Natl Med Assoc 2002; 94: 1 - 26 [PubMed].. [PubMed]

2. Mechanick JI, Zhao S, Garvey WT. The Adipokine-Cardiovascular-Lifestyle Network: Translation to Clinical Practice. J Am Coll Cardiol 2016; 68: 1785 - 803. [PubMed][CrossRef]

3. Curtis T, Kvernmo S, Bjerregaard P. Changing living conditions, life style and health. Int J Circumpolar Health 2005; 64: 442 - 50. [PubMed][CrossRef]

4. Casali ME, Borsari L, Marchesi I et al. Lifestyle and food habits changes after migration: a focus on immigrant women in Modena (Italy). Ann Ig 2015; 27: 748 - 59 [PubMed].. [PubMed]

5. Prabhakar PK, Kumar A, Doble M. Combination therapy: a new strategy to manage diabetes and its complications. Phytomedicine 2014; 21: 123 - 30. [PubMed] [CrossRef]

6. Legemidler til behandling av makrovaskulære senkomplikasjoner ved diabetes. Nasjonal faglig retningslinje for diabetes 2016. https://helsedirektoratet.no/retningslinjer/diabetes (16.10.2017).

7. Ahmed E, El-Menyar A. South Asian ethnicity and cardiovascular risk: the known, the unknown, and the paradox. Angiology 2015; 66: 405 - 15. [PubMed][CrossRef]

8. Bilen O, Kamal A, Virani SS. Lipoprotein abnormalities in South Asians and its association with cardiovascular disease: Current state and future directions. World J Cardiol 2016; 8: 247 - 57. [PubMed][CrossRef]

9. Bansal SK, Agarwal S, Daga MK. Conventional and advanced lipid parameters in premature coronary artery disease patients in India. J Clin Diagn Res 2015; 9: BC07 - 11 [PubMed].. [PubMed]

10. Guo L, Zhang LL, Zheng B et al. The C825T polymorphism of the G-protein β3 subunit gene and its association with hypertension and stroke: an updated meta-analysis. PLoS One 2013; 8: e65863. [PubMed][CrossRef]

11. Kato N. Ethnic differences in genetic predisposition to hypertension. Hypertens Res 2012; 35: 574 - 81. [PubMed][CrossRef]

12. Johnson JA. Ethnic differences in cardiovascular drug response: potential contribution of pharmacogenetics. Circulation 2008; 118: 1383 - 93. [PubMed] [CrossRef]

13. Tziomalos K, Weerasinghe CN, Mikhailidis DP et al. Vascular risk factors in South Asians. Int J Cardiol 2008; 128: 5 - 16. [PubMed][CrossRef]

14. Gupta M, Singh N, Verma S. South Asians and cardiovascular risk: what clinicians should know. Circulation 2006; 113: e924 - 9. [PubMed][CrossRef]

15. Bakker LE, Sleddering MA, Schoones JW et al. Pathogenesis of type 2 diabetes in South Asians. Eur J Endocrinol 2013; 169: R99 - 114. [PubMed][CrossRef]

16. Kulkarni KR, Markovitz JH, Nanda NC et al. Increased prevalence of smaller and denser LDL particles in Asian Indians. Arterioscler Thromb Vasc Biol 1999; 19: 2749 - 55. [PubMed][CrossRef]

17. Bathula R, Hughes AD, Panerai R et al. Indian Asians have poorer cardiovascular autonomic function than Europeans: this is due to greater hyperglycaemia and may contribute to their greater risk of heart disease. Diabetologia 2010; 53: 2120 - 8. [PubMed][CrossRef]

18. Park CM, Tillin T, March K et al. Hyperglycemia has a greater impact on left ventricle function in South Asians than in Europeans. Diabetes Care 2014; 37: 1124 - 31. [PubMed][CrossRef]

19. Schofield P, Saka O, Ashworth M. Ethnic differences in blood pressure monitoring and control in south east London. Br J Gen Pract 2011; 61: 190 - 6. [PubMed][CrossRef]

20. Brewster LM, van Montfrans GA, Kleijnen J. Systematic review: antihypertensive drug therapy in black patients. Ann Intern Med 2004; 141: 614 - 27. [PubMed][CrossRef]

21. Peck RN, Smart LR, Beier R et al. Difference in blood pressure response to ACE-Inhibitor monotherapy between black and white adults with arterial hypertension: a meta-analysis of 13 clinical trials. BMC Nephrol 2013; 14: 201. [PubMed][CrossRef]

22. Dong Y, Zhu H, Sagnella GA et al. Association between the C825T polymorphism of the G protein β3-subunit gene and hypertension in blacks. Hypertension 1999; 34: 1193 - 6. [PubMed][CrossRef]

23. Siffert W, Forster P, Jöckel KH et al. Worldwide ethnic distribution of the G protein β3 subunit 825T allele and its association with obesity in Caucasian, Chinese, and Black African individuals. J Am Soc Nephrol 1999; 10: 1921 - 30 [PubMed].. [PubMed]

24. Levy R. Medication use by ethnic and racial groups: policy implications. J Pharm Health Serv Res 2010; 1: 15 - 22.

25. Type 2 Diabetes: National Clinical Guideline for Management in Primary and Secondary Care (Update). National Collaborating Centre for Chronic Conditions (UK). London: Royal College of Physicians (UK), 2014.

26. Egan BM, Bandyopadhyay D, Shaftman SR. Treatment of hypertension in blacks. UpToDate. https://www.uptodate.com/contents/treatment-of-hypertension-in-blacks (16.10.2017).

27. Liao JK. Safety and efficacy of statins in Asians. Am J Cardiol 2007; 99: 410 - 4. [PubMed][CrossRef]

28. IRIS Study Group. Comparison of rosuvastatin versus atorvastatin in South-Asian patients at risk of coronary heart disease (from the IRIS Trial). Am J Cardiol 2007; 99: 1538 - 43. [PubMed][CrossRef]

29. ARIES Study Group. Comparison of efficacy and safety of rosuvastatin versus atorvastatin in African-American patients in a six-week trial. Am J Cardiol 2006; 97: 229 - 35. [PubMed][CrossRef]

30. Lee E, Ryan S, Birmingham B et al. Rosuvastatin pharmacokinetics and pharmacogenetics in white and Asian subjects residing in the same environment. Clin Pharmacol Ther 2005; 78: 330 - 41. [PubMed][CrossRef]

31. Harper CR, Jacobson TA. Evidence-based management of statin myopathy. Curr Atheroscler Rep 2010; 12: 322 - 30. [PubMed][CrossRef]

32. Zhang H, Plutzky J, Skentzos S et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med 2013; 158: 526 - 34. [PubMed][CrossRef]

33. Ramsey LB, Johnson SG, Caudle KE et al. The clinical pharmacogenetics implementation consortium guideline for SLCO1B1 and simvastatin-induced myopathy: 2014 update. Clin Pharmacol Ther 2014; 96: 423 - 8. [PubMed][CrossRef]

34. Gupta A, Thompson PD. The relationship of vitamin D deficiency to statin myopathy. Atherosclerosis 2011; 215: 23 - 9. [PubMed][CrossRef]

35. Mergenhagen K, Ott M, Heckman K et al. Low vitamin D as a risk factor for the development of myalgia in patients taking high-dose simvastatin: a retrospective review. Clin Ther 2014; 36: 770 - 7. [PubMed][CrossRef]

36. Glueck CJ, Abuchaibe C, Wang P. Symptomatic myositis-myalgia in hypercholesterolemic statin-treated patients with concurrent vitamin D deficiency leading to statin intolerance may reflect a reversible interaction between vitamin D deficiency and statins on skeletal muscle. Med Hypotheses 2011; 77: 658 - 61. [PubMed][CrossRef]

37. Zhou YT, Yu LS, Zeng S et al. Pharmacokinetic drug-drug interactions between 1,4-dihydropyridine calcium channel blockers and statins: factors determining

interaction strength and relevant clinical risk management. Ther Clin Risk Manag 2014; 10: 17 - 26 [PubMed].. [PubMed]

38. Enas EA, Pazhoor HC, Kuruvila A et al. Intensive statin therapy for Indians: Part-I. Benefits. Indian Heart J 2011; 63: 211 - 27 [PubMed].. [PubMed]

39. Stamler J, Vaccaro O, Neaton JD et al. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993; 16: 434 - 44. [PubMed][CrossRef]

40. Tandon N, Ali MK, Narayan KM. Pharmacologic prevention of microvascular and macrovascular complications in diabetes mellitus: implications of the results of recent clinical trials in type 2 diabetes. Am J Cardiovasc Drugs 2012; 12: 7 - 22. [PubMed][CrossRef]

41. Shah A, Kanaya AM. Diabetes and associated complications in the South Asian population. Curr Cardiol Rep 2014; 16: 476. [PubMed][CrossRef]

42. Agyemang C, Addo J, Bhopal R et al. Cardiovascular disease, diabetes and established risk factors among populations of sub-Saharan African descent in Europe: a literature review. Global Health 2009; 5: 7. [PubMed][CrossRef]

43. Lee SM. A review of language and other communication barriers in health care. Washington D.C.: U.S. Department of health and human services/Office of minority health, 2003.

44. Joseph-Williams N, Elwyn G, Edwards A. Knowledge is not power for patients: a systematic review and thematic synthesis of patient-reported barriers and facilitators to shared decision making. Patient Educ Couns 2014; 94: 291 - 309. [PubMed] [CrossRef]

Publisert: 28. November 2017. Tidsskr Nor Legeforen. DOI: 10.4045/tidsskr.16.0680
Received 18.8.2016, first revision submitted 27.1.2017, accepted 16.10.2017.