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This document is divided into two parts

1) The **HIGHLIGHTS AND *EDITORIAL COMMENTS* SECTION**

HIGHLIGHTS condenses the contents of studies, and allows a quick review of pertinent points of each article.

EDITORIAL COMMENTS *are the editor's assessments of the clinical practicality of articles based on his long-term review of the current literature and his 25-year publication of Practical Pointers.*

2) The main **ABSTRACTS** section is designed as a reference. It presents structured summaries of the contents of articles in much more detail.

I hope you will find *Practical Pointers* interesting and helpful. The complete content of all issues for the past 10 years can be accessed at www.practicalpointers.org

Richard T. James Jr. M.D.
Editor/Publisher.

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HIGHLIGHTS AND *EDITORIAL COMMENTS* JUNE 2010

Risk Scores Will Inevitably Become Outdated

6-1 AN INDEPENDENT AND EXTERNAL VALIDATION OF QRISK2 CARDIOVASCULAR DISEASE RISK SCORE

"General practitioners need an accurate and reliable tool to help them identify patients at high risk of having a cardiovascular event." Many risk scores have been developed to estimate 10-year risk based on known risk factors.

After development of a score, it must be externally validated. This article describes results of the validation of a new risk score (**QRISK2**)

In the UK, until recently, NICE recommended use of the long-established Framingham equation. Subsequently, NICE developed an adjusted version of Framingham (**N-F**).

In this study, participants were patients registered in the UK database between 1993 and 2008. The cohort consisted of 1 583 106 patients among 365 general practices (median age 48; IQR 41-59). Median follow-up = 6.2 years.

Primary outcome = first diagnosis of cardiovascular disease (MI, angina, coronary heart disease, stroke, transient ischemic attack).

The incidence of CVD varied widely between different ethnic groups.

Risk classification used a 20% or greater risk of a CVD event over the next 10 years. (The cutpoint used in the UK to treat with statins.)

Calculated QRISK2 score (10-year estimated risk of CVD). Determined actual observed incidence of CVD. Calculated how many patients would be reclassified using QRISK2 compared with N-F:

Among men, predicted to be at high risk (>20%) of a CVD event, actual incidence of CVD per 1000 patient-years was 27.8 with QRISK2, and 21.9 with N-F. Among women, incidence was 24.3 and 21.9

A total of 11.6% would be reclassified:

1.8% classified as low risk (<20% by QRISK2) with N-F would be upgraded to high risk with QRISK2. 45% classified as high risk by N-F would be downgraded to low risk by QRISK2. N-F grossly over-estimated risk

The actual observed risk of CVD in these patients was 14.00%. The mean predicted high-risk by QRISK2 was 14.98%, and the mean predicted high-risk by N-F was 25.14%

Risk scores will inevitably become outdated with improvements in clinical outcomes and data recording, and changes in population demographics. QRISK2 will undergo annual upgrades.

Conclusion: QRISK2 is more accurate than N-F in predicting a high-risk population in the UK.

I congratulate the investigators on completion of this massive cohort study.

In the UK, the cutpoint of 20% risk of CVD over the next 10 years is used to determine drug treatment. Those with 20% or more risk should be treated with drugs (usually statins). Those between 10% and 20% are doubtful. Those under 10% should not be treated.

My main reason for abstracting this study was to ask--How valuable are risk scores such as these for primary care practice in the US? How often do primary care physicians in the US use risk calculators? Do risk scores have much effect on clinical decision-making? Do they improve clinical outcomes? I doubt clinicians in the US use them very often. They will be more likely to treat individual risks, including dyslipidemia at an early age. And treat all risks simultaneously.

Primary care looks far beyond 10 years. The atherosclerotic process begins at an early age.

It is possible for a younger patient who has a high cholesterol to have a low score. And an obese, hypertensive patient to have a score under 20%.

Older patients often have high scores determined mainly by age.

The Framingham score has had a remarkable durability. After decades, it is still frequently quoted. I believe it is now outdated.

Risk scores may be useful in encouraging patients to adopt a more healthful lifestyle, and to be more compliant with treatment. Patients with high scores might be more likely to improve lifestyles and be more compliant with taking their medications.

Quantifying The Risks And Benefits Of Statins At The Population Level.

6-2 UNINTENDED EFFECTS OF STATINS IN MEN AND WOMEN IN ENGLAND AND WALES

This large population-based study examined a range of clinical outcomes that are positively and negatively associated with statin use.

A prospective study, derived from a computer-based medical information system (2002-2008) in the UK, included patients (age 30-84).

Identified new users of statins during the study period, with the remaining patients classified as non-users. Classified statin use by the type of statin first prescribed.

Calculated the number needed to treat to benefit one patient **(NNT**) and the number needed to treat to harm one patient (**NNH**) over 5 years for patients at high risk of cardiovascular disease. It was based on a QRISK2 score indicating a risk of 20% a CVD event over the next 10 years, the group eligible for statin treatment in the UK.

. Included 368 practices with a total of 2 121 786 patients age 30-84 at study entry:

1 778 770 had not been prescribed statins: 225 992 were new users. The majority received simvastatin. The remainder received: atorvastatin, fluvastatin, pravastatin and rosuvastatin.

The associations between statins and Parkinson disease; rheumatoid arthritis; venous thrombo-embolism; gastric, lung, renal, breast and prostate cancers; and melanoma were not significant.

Adverse effects significantly associated with statins:

Cataracts, moderate or serious liver dysfunction, acute renal failure, and myopathy:

Beneficial effects significantly associated with statins:

Cardiovascular disease and esophageal cancer:

Numbers needed to treat to *benefit* one patient (NNT) over 5 years:

Women	NNT	No per 10 000
CVD Event	37	271
Esophageal cancer	1266	8
Men		
CVD event	33	301
Esophageal cancer	1082	9

Numbers needed to treat to *harm* one patient (NNH) over 5 years:

Women	NNH	No. per 10 000
Cataract	33	307
Liver dysfunction	136	74
Myopathy `	259	39
Acute renal failure	434	23
Men		
Cataract	52	191
Myopathy	91	110
Liver dysfunction	142	71
Acute renal failure	346	29

All risks persisted during treatment and were highest in the first year of treatment. After stopping treatment, risks returned to normal within 1 to 3 years, except for myopathy, which did not abate.

Adverse effects tended to be similar across all types of statins. The risk of liver dysfunction was

highest with fluvastatin. The risk of liver dysfunction, acute renal failure, and possibly myopathy were dose-related. As liver dysfunction is common and the other two outcomes are life threatening, the findings tend to support a policy of using lower doses of statins in people at high risk for the adverse effects.

This study adds important data. The large data-base increases validity and generalizability.

We need to know how common adverse effects of statins are The list of diseases not associated with statins is reassuring, as is the observation that risk returns to normal after a year or two.

Statins are among the safest drugs we use. They are not innocuous. In general,, over a 5-year period, between 2 in 1000 and 11 per 1000 will be harmed. For cataracts, the harm is up to 3 per 100. We must be alert for these effects. (This is my first encounter with the risk of cataracts associated with statins.)

At some point, depending on individual risk of CVD, harm may outweigh benefit. This may occur in the very young and the very old.

Drug companies tout the strength of their statins, stating that they reduce LDL-cholesterol more than their competitors. Pushing the dose to obtain lower LDL-c levels may increase adverse effects. I believe "go slow and go low", while observing the effect, applies to statins.

"Dietary Management Is Appropriate For All Patients with Hypertension"

6-3 DIETARY THERAPY IN HYPERTENSION

THE CLINICAL PROBLEM

"Morbidity increases among persons whose blood pressure is above 115/75."

The prevalence of hypertension increases dramatically with age, from about 10% in persons age 30, to 50% in age 60. However, some persons, including strict vegetarians, and those whose sodium intake is low, have virtually no increases in hypertension with age.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

The 3 corners of dietary treatment--a healthful diet, reduced sodium intake, and reduced body fat--influence the pathophysiology at many points of hypertension control.

High sodium intake is strongly correlated with the development of hypertension. It leads to increased intravascular fluid volume, cardiac output, peripheral resistance and higher BP.

Other factors contribute to pathophysiology of hypertension:

Stiffening of large conduit arteries in the elderly.

Vasoconstriction due to endothelial dysfunction and proliferation of smooth-muscle cells in small vessels.

Increased activity of the sympathetic nervous system.

Both aging and obesity contribute.

Reduction in salt intake and weight loss are effective in lowering BP.

Decreases in abdominal visceral fat improves function of both conduit and resistance vessels.

CLINICAL EVIDENCE

The Dietary Approaches to Stop Hypertension (DASH) was especially effective in patients who had hypertension. When combined with low salt intake, benefit was greater. When weight loss was added to the diet, BP was reduced to a greater extent.

Sodium reduction, the DASH diet (vs controls), and changes in systolic BP:

Sodium	Controls	DASH
3.5 g daily	143 mm Hg	135 mm Hg
2.3 g	141	133
1.2 g	135	128

(Note the systolic BP of the controls was also lowered by salt restriction.)

CLINICAL USE

Dietary management is appropriate for all patients with hypertension, and for those with pre-hypertension. In simple terms:

Eat poultry, fish, nuts, legumes, low-fat and non-fat dairy, vegetables, fruit, whole grains poly - unsaturated and mono-unsaturated fats (olive, canola, soybean, peanut, corn, sunflower, safflower oil)

Avoid red meat, full fat dairy, snacks and desserts high in sugars, white flour, butter, coconut oil, palm-kernel oil, sweetened beverages, candies, and cookies. Canned and processed foods should be limited unless their salt content has been eliminated

GUIDELINES

1.5 g sodium per day (~ 4 g salt) is optimal. A BMI less than 25 is also recommended. Alcohol intake is limited.

"A trial of intensive dietary treatment is warranted for 6 months to try to achieve the target goal for blood pressure (systolic < 140 and diastolic < 90) before medication is introduced."

Patients should monitor their BP at home.

These dietary recommendations are almost identical (except for stricter sodium content) to diets recommended for atherosclerotic disease. However, I believe few (if any) patients with hypertension treated in primary care would continue a greatly reduced sodium and calorie diet. Some strict vegetarians will have less of a problem.

Why? Humans naturally crave sweets and salt. Our children are reared using sweets as a "treat' and "reward". They contain high levels of sodium and sugar. Craving is both in-born and fostered by our society. The same difficulty exists for diets to control weight.

However, even a modest reduction in salt may benefit.

The article did not mention the helpful role of potassium in BP control As sodium content of the diet decreases, potassium increases to add to therapeutic benefit.

A greatly reduced sodium diet may be harmful in some (especially older) patients who are being treated with diuretics and become dehydrated.

The authors recommend dietary treatment for 6 months before drug therapy is started. I doubt many primary care clinicians will follow this advice. Diet is unlikely to be followed, and unlikely to succeed in reducing BP. Primary care physicians will avoid temporizing with drug treatment.

Importance Of Maintaining Optimal Weight During Middle Age For Prevention Of Diabetes

6-4 ASSOCIATION BETWEEN ADIPOSITY IN MIDLIFE AND OLDER AGE AND RISK OF DIABETES IN OLDER ADULTS.

This prospective population-based cohort study of older adults examined the relationship between measures of overall body fat, body fat distribution, changes in these measures, and risk of DM-2 in older adults.

Entered (1989-1990), a group of 5201 ambulatory, non-institutionalized men and women age 65 and older (mean = 73). After exclusions for diabetes and other reasons, a cohort of 4193 remained.

At baseline and periodically thereafter, collected comprehensive information on health-related variables. Self-reported body weight at age 50 was collected at baseline.

Periodically determined height, body weight, and waist circumference (**WC**).

Calculated body mass index (**BMI**) from the self-reported weight at age 50 and the measured height at baseline. Determined BMI at baseline from measured weight and height. Classified participants as having DM-2 if fasting glucose was 126 mg/dL and above.

Over a median follow-up of 12 years, 339 new cases of DM-2 occurred among 4193 participants.

BMI at baseline, BMI at age 50, and waist circumference were strongly related to risk of developing DM-2.

Association between baseline measures of adiposity and risk of incident DM-2 in men 1989-2007.:

BMI quintiles	<23.3	23.3 - 25.0	26.1 - 26.6	26.7 - 28.6	>28.6
Hazard ratio (**HR**) for DM-2	1.00	1.9	2.9	4.4	5.6
Waist circumference (cm)	< 89.1	89.1 - 94.0	94.1 - 99.0	99.1 - 104.5	>104.5
HR for DM-2	1.00	2.1	2.2	3.9	5.1

(Ie, men with higher BMI and WC at baseline were much more likely to develop DM-2. Women had similar associations)

Participants in the highest category of adiposity had approximately 2- to 6- fold increased risk of developing DM-2 compared with those in the lowest category.

"We found that measures of overall and central adiposity were strongly associated with the risk of incidental diabetes in both men and women." Weight gain during midlife (after age 50) and in late life (after age 65) is an important risk factor for diabetes among older adults.

It is possible that regional fat distribution is more important in the etiology of diabetes than absolute fat mass. Visceral fat and thigh fat are associated with impaired glucose tolerance and diabetes in older adults independent of total adiposity.

This analysis showed an association between waist circumference and diabetes risk in individuals with a BMI less than 25, suggesting that measurement of waist circumference may add important information beyond BMI regarding diabetes risk in normal weight individuals.

Conclusion: Among older adults, overall and central adiposity, and weight gain during middle age and after age 65 were associated with increased risk of diabetes.

The study emphasizes importance of:

1. Entering late middle-age with a normal BMI and waist circumference.

2. Controlling weight and waist circumference before age 50, and after ages 50 and 65.

3. Controlling waist circumference at any age, including individuals with BMI below 25.

These risk factors apply to cardiovascular disease and hypertension as well.

Less Frequent Tooth Brushing--More Periodontal Disease--Higher Risk of CVD

6-5 TOOTH BRUSHING, INFLAMMATION, AND RISK OF CARDIOVASCULAR DISEASE: RESULTS FROM A SCOTTISH HEALTH STUDY

There has been increasing interest in a possible link between dental disease, specifically periodontal disease (**PD**), and CVD. Inflammation plays an important link in the pathogenesis of atherosclerosis.

Poor oral hygiene is the major cause of PD, a chronic infection of the tissue surrounding the teeth. It is one of the most common chronic infections and is associated with a moderate systemic inflammatory response such as raised concentrations of C-reactive protein and other inflammatory markers.

This study examined whether self-reported tooth brushing behavior is associated with increased markers of inflammation and CVD.

The Scottish Health Study is a cross sectional survey of a nationally representative sample of the general population living in Scottish households.

Interviewers visited households and collected data on demographics, medical history, and health behaviors, including oral health. Oral health behavior was assessed from self-reported frequency of visits to a dentist, and tooth brushing (twice daily, once daily and less than once a day.)

The final sample size was 11 869

Linked the database to hospital admissions and deaths. Primary endpoint = composite of fatal and non-fatal CVD. There were 555 CVD events over an average of 8 years.

Poor oral hygiene habits were more prevalent in middle-aged men and were associated with other CVD risks such as smoking, obesity, and hypertension.

Model of tooth brushing and CVD:

Tooth brushing	Hazard ratio (adjusted for multiple possible confounders)\
Twice a day	1.00 (reference)
Once a day	1.3
< Once a day	1.7

There were significant associations between frequency of tooth brushing and markers of low grade inflammation. Levels of C-reactive protein rose from 3.07 mg/L to 4.18 mg/L as frequency of tooth brushing declined. Fibrinogen levels rose from 2.86 g/L to 2.98 g/L

In this study, participants who brushed their teeth less often had a 70% increase in risk of CVD events compared with frequent brushers.

Doctors should be alert to the possible oral source of an increased inflammatory burden.

While this study was not definitive, it was provocative. And, I believe, important clinically. Few studies use a proxy observation to link with a clinical endpoint.

The strength of the study lies in the large study-group of representative individuals in the Scottish population. This increase generalizability

The advice regarding the importance of recognizing PD as a general health problem is worth while in itself. Primary care clinicians should include inspection of the mouth in the physical examination. And urge their patients (especially middle-aged males) to adopt good dental hygiene and regular visits to the dentist.

The study strengthens the association between PD and CVD, which has been noted for years.

Oseltamivir Ring Chemoprophylaxis Was Effective In Reducing an Outbreak of 2009 H1N1 Flu

6-6 OSELTAMIVIR RING PROPHYLAXIS FOR CONTAINMENT OF 2009 H1N1 INFLUENZA OUTBREAKS.

This study describes the Singapore experience in responding to 4 outbreaks of 2009 pandemic influenza A (H1N1) virus in military camps and evaluates the role of oseltamivir "ring chemoprophylaxis" in attenuating transmission of the virus.

A suspected case of influenza was defined as influenza-like illness (temperature 38^{o} or more, with cough or sore throat) with onset of symptoms within 7 days after travel to an affected area, close contact with a person with confirmed infection, or contact with a local cluster of infected persons.

Prompt laboratory confirmation was by polymerase-chain-reaction.

Contacts were defined as persons who had unprotected exposure to an infected person since the day before to onset of symptoms. Most contacts were quarantined at home for 7 days.

A 10-day course of *Tamiflu* was administered to coworkers for 10 days after exposure to an infected person. (Coworker defined as a member of the same military unit where contact opportunities were substantial. Larger prophylaxis rings were instituted if cases were present in multiple units.

. Summary of 4 outbreaks:

Total number of personnel	1175
Confirmed cases	82 (7%)
Before intervention	75 (6.4%)
After intervention	7 (0.6%)

(After prophylaxis began, in combination with home leave to avoid contacts, only 7 more cases were confirmed.)

All 7 cases with onset after prophylaxis occurred within 4 days after the intervention.

Adverse effects of oseltamivir: 8% reported mild, non-respiratory symptoms. There were no neuropsychiatric events; no severe adverse events reported.

"In the present study, we have shown that ring prophylaxis with oseltamivir, given after

exposure in military camps was effective, allowing training and operations to continue while substantially reducing the risk of further generations of cases during prophylaxis."

Ring prophylaxis based on spatial proximity was more effective in controlling the spread of disease than was the focus on close contacts.

Early case detection and use of antiviral ring prophylaxis effectively truncated the spread of infection during an epidemic. Aggressive prophylaxis may be justifiable to protect vulnerable populations such as frail or elderly residents of long-term care facilities, or persons in closed communities.

Conclusion: Oseltamivir ring chemoprophylaxis, together with prompt identification and isolation of infected personnel, was effective in reducing the impact of the outbreak of 2009 H1N1 influenza in semi-closed settings.

Application of ring prophylaxis and quarantine would, of course, be much more difficult in primary care practice the in the military.

I believe ring prophylaxis is a valuable intervention to contain epidemics. It may be especially effective in controlling flu in hospitals, nursing homes, retirement communities, and in air travelers.

In households of a case of flu, prophylaxis of the entire family may prevent infection and allow members who must work outside the home to protect their contacts.

Ring prophylaxis does not act alone. Isolation and quarantine are essential. Vaccination is essential. Prophylaxis may be of value in years when the vaccine is a poor match for the circulating virus.

ABSTRACTS JUNE 2010

Risk Scores Will Inevitably Become Outdated

6-1 AN INDEPENDENT AND EXTERNAL VALIDATION OF QRISK2 CARDIOVASCULAR DISEASE RISK SCORE

"General practitioners need an accurate and reliable tool to help them identify patients at high risk of having a cardiovascular event." Many risk scores have been developed to estimate 10-year risk based on known risk factors.

In the UK, until recently, NICE[1] recommended use of the long established Framingham[2] equation. Subsequently, NICE developed an adjusted version of Framingham (**N-F**).[3]

QRISK2[4], developed in the UK, is the latest risk score.

NICE has now ceased to recommend any single score, leaving clinicians to choose the tool they consider the most appropriate.

After development of a score, it must be externally validated. This article describes results of the validation.

STUDY

1. Participants were patients registered in the UK database between 1993 and 2008.
2. Excluded those with a prior diagnosis of cardiovascular disease (**CVD**), and persons under age 34, and over age 74. None had been prescribed statin drugs.
3. Primary outcome = first diagnosis of cardiovascular disease (MI, angina, coronary heart disease, stroke, transient ischemic attack).
4. Risk classification used a 20% threshold for estimated risk over the next 10 years. The investigators calculated how many patients would be reclassified using QRISK2 compared with N-F: And determined the actual observed incidence of CVD.

RESULTS

1. The cohort consisted of 1 583 106 patients (1993-2008) among 365 general practices. Median follow-up = 6.2 years; median age 48; IQR 41-59.
2. In total, there were 71 465 incident cases of CVD, from 9.4 million person-years of observation.
3. The incidence of CVD varied widely between different ethnic groups. The age-standardized rates per 1000 person-years were 5.89 for white women and 9.20 for white men. The highest rates were among South Asian groups. Among Pakistani men, the rate was 19.55 per 1000 person-years.

4. Calculated QRISK2 score (10-year estimated risk of CVD). Determined actual observed incidence of CVD. Calculated how many patients would be reclassified using QRISK2 compared with N-F:

   Among men, predicted to be at high risk (>20%) of a CVD event, actual incidence of CVD per 1000 patient-years was 27.8 with QRISK2, and 21.9 with N-F. Among women, incidence was 24.3 and 21.9

5. A total of 11.6% would be reclassified:

   1.8% classified as low risk (<20%) with N-F would be upgraded to high risk with QRISK2.

   45% classified as high risk by N-F would be downgraded to low risk by QRISK2.

   N-F grossly over-estimated risk

6. The actual observed risk of CVD in these patients was 14.00%. The mean predicted high-risk by QRISK2 was 14.98%, and the mean predicted high-risk by N-F was 25.14%

DISCUSSION

1. "This constitutes one of the largest groups of patients used to develop and externally validate a risk score before its recommendation and implementation in clinical practice."
2. In this large cohort of 1.6 million patients, QRISK2 had a superior performance in predicting risk of CVD. The N-F over-predicted the 10-year risk compared with the more accurate QRISK2.
3. The original Framingham was developed on a small homogeneous group (n = 5573) of white persons sampled from a single town in the US between 1968- 1975.
4. Risk scores will inevitably become outdated with improvements in clinical outcomes and data recording, and changes in population demographics. QRISK2 will undergo annual upgrades.

CONCLUSION

QRISK2 is more accurate than N-F in predicting a high-risk population in the UK.

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A short version appeared in BMJ June 15, 2010; 340:1231 First author Gary S Collins, University of Oxford, Oxford, UK

1 National Institute for Health and Clinical Excellence (UK)

2 Original Framingham (5 items)

- Age
- Gender
- Total cholesterol

4 QRISK2 added:

- Body mass index
- Family history (1st degree relative < age 60)
- Deprivation score (Townsend score is on Google)

Smoking
Systolic BP

3 N-F added :

Total cholesterol / HDL-cholesterol ratio
Left ventricular hypertrophy
Type 2 diabetes
Age x type 2 diabetes
Age x left ventricular hypertrophy
Age x sex
Treated hypertension
Ethnicity
Rheumatoid arthritis
Atrial fibrillation
Renal disease
Most were age-modified
(QRISK2 calculator is on Google)

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Quantifying The Risks And Benefits Of Statins At The Population Level.

6-2 UNINTENDED EFFECTS OF STATINS IN MEN AND WOMEN IN ENGLAND AND WALES

Statins are among the most widely prescribed drugs. Both their intended and unintended effects and how these vary by type of drug, dose, and duration of use need to be quantified.

This large population-based study examined a range of clinical outcomes that are positively and negatively associated with statin use.

STUDY

1. This prospective study, derived from a computer-based medical information system (2002-2008) in the UK, included patients (age 30-84).
2. Main outcome measures: first recorded occurrence of a CVD event, moderate or severe myopathic events (diagnosis of myopathy or rhabdomyolysis or a raised creatine kinase 4 or more times upper normal), moderate or severe liver dysfunction (alanine transaminase over 3 times normal), acute renal failure, cataracts, common cancers, and others.
3. Identified new users of statins during the study period, with the remaining patients classified as non-users. Classified statin use by the type of statin first prescribed.
4. When the hazard ratio (**HR**) was less than 0.80 or more than 1.20, and was statistically significant, the effect was considered to be significant.
5. Calculated the number needed to treat to benefit one patient **(NNT**) and the number needed to treat to

harm one patient (**NNH**) over 5 years for patients at high risk of cardiovascular disease. It was based on a QRISK2 score indicating a risk of 20% a CVD event over the next 10 years, the group eligible for statin treatment in the UK.

RESULTS

1. Included 368 practices with a total of 2 121 786 patients age 30-84 at study entry:

   1 778 770 had not been prescribed statins: 225 992 were new users. The majority received simvastatin. The remainder received: atorvastatin, fluvastatin, pravastatin and rosuvastatin.

2. Compared with non-users, new users tended to be older, more likely to be men, and to have comorbidities such as atrial fibrillation, cardiovascular disease, peripheral vascular disease, treated hypertension, diabetes, and chronic kidney disease.

3. The associations between statins and Parkinson disease; rheumatoid arthritis; venous thrombo-embolism; gastric, lung, renal, breast and prostate cancers; and melanoma were not significant.

4. Adverse effects significantly associated with statins:

   A. Cataracts:

      Each statin was associated with an increase in risk. There was no evidence of a dose-response relation. Risk was increased within a year of starting, persisted during treatment, and returned to normal in one year after discontinuation.

   B. Moderate or serious liver dysfunction:

      All statins were associated with liver dysfunction. Fluvastatin had the highest HR: 2.5 compared with no statin. For simvastatin the HR was1.5.

      Risk was highest within the first year of treatment. The risk persisted during treatment, and returned to normal in 1 to 3 years after discontinuation.

   C. Acute renal failure:

      Risk increased in both men and women. Risk was evident within one year and persisted for the first 5 years of treatment, and returned to normal 1-3 years after discontinuation.

   D. Moderate or serious myopathy:

      Risk was increased in both men and women, but was higher in men.

      All statins were associated with increased risk of myopathy. The risk was highest within the first year of starting treatment.

      The risk persisted during treatment and *continued* after stopping. At 3 years after stopping

risk was still evident.

5. Beneficial effects significantly associated with statins:

A Cardiovascular disease:

Treatment with statins was based on a 20% cutpoint for risk of a CVD event over the next 10 years determined by the QRISK2 score.

Women:

The NNT with any statin to prevent one case of CVD over the next 5 years = 37

The estimated number of prevented cases per 10 000 patients treated = 271

Men

The NNT with any statin to prevent one case of CVD over the next 5 years = 33

The estimated number of prevented cases per 10 000 patients treated = 301

B. Esophageal cancer:

Risk *decreased* in men and women using simvastatin and atorvastatin and in men receiving atorvastatin. The decrease was evident within 1 to 3 years, and returned to normal within one year.

6. Risks of significant adverse outcomes — Adjusted HR compared with no statin (HR = 1.00)

	Women	Men
A. Moderate or severe myopathy		
Simvastatin	3.9	6.1
B. Acute renal failure		
Simvastatin	1.5	1.6
C. Cataract		
Simvastatin	1.3	1.3
D. Moderate or severe liver dysfunction		
Simvastatin	1.5	1.5

Risk was increased for other statins as well.

7. Numbers needed to treat to benefit one patient (NNT) over 5 years:

Women	NNT	No per 10 000
CVD Event	37	271
Esophageal cancer	1266	8
Men		
CVD event	33	301
Esophageal cancer	1082	9

8. Numbers needed to treat to harm one patient (NNH) over 5 years:

Women	NNH	No. per 10 000
Cataract	33	307
Liver dysfunction	136	74
Myopathy	259	39
Acute renal failure	434	23
Men		
Cataract	52	191
Myopathy	91	110
Liver dysfunction	142	71
Acute renal failure	346	29

DISCUSSION

1. This study was large, prospective, and included many potential confounders. It was carried out in a setting where patients in the UK are assessed, treated, and followed-up. It is likely to be generalisable.
2. "We were able to quantify adverse effects associated with statins, including myopathy, liver dysfunction, acute renal failure, and cataract." These seemed to be class effects with a dose-response apparent only for acute renal failure and cataract.
3. All risks persisted during treatment and were highest in the first year of treatment. After stopping treatment, risks returned to normal within 1 to 3 years, except for myopathy.
4. This study differed from previous studies. It compared new users with non-users, and used more inclusive outcome definitions and identified many more cases.
5. Observational studies, with their large representative and ethnically diverse populations, have limitations, notably bias and unmeasured confounding.
6. At a national level, the study is likely to be useful for policy and planning purposes because it gives the expected numbers of additional adverse events per 10 000 patients that would occur if all patients likely to be at high risk of CVD were prescribed statins.
7. Adverse effects tended to be similar across all types of statins. The risk of liver dysfunction was highest with fluvastatin. The risk of liver dysfunction, acute renal failure, and possibly myopathy were dose-related. As liver dysfunction is common and the other two outcomes are life threatening, the findings tend to support a policy of using lower doses of statins in people at high risk for the adverse effects.

8. The study was not designed to show causality.

SUMMARY

The study quantifies the risks and benefits of statins at the population level so that they can be applied at the individual level.

BMJ 2010;340:c2197 doi: 10.1136/bmj.c2197
A condensed version appeared in BMJ June 5, 2010;340:1232 first author Julia Hippisley-Cox, University Park, Nottingham, UK

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"Dietary Management Is Appropriate For All Patients with Hypertension"

6-3 DIETARY THERAPY IN HYPERTENSION

THE CLINICAL PROBLEM

"Morbidity increases among persons whose blood pressure is above 115/75."

"Systolic blood pressure above 115 mg Hg is the most important determinant of the risk of death worldwide, being responsible for 7.6 million cardiovascular deaths annually."

From 1960 through 1991, BP declined in the US, and after the first 10 years of this interval, the rate of cardiovascular deaths decreased. However, from 1990 through 2002, BP increased. Intake of fruits and vegetables and adherence to healthful dietary patterns declined during this period, and the prevalence of abdominal obesity increased. Both trends have contributed to hypertension.

The prevalence of hypertension increases dramatically with age, from about 10% in persons age 30 to 50% in age 60. However, some persons, including strict vegetarians, and those whose sodium intake is low, have virtually no increases in hypertension with age.

PATHOPHYSIOLOGY AND EFFECT OF THERAPY

The pathophysiology of essential hypertension is complex.

The 3 corners of dietary treatment--a healthful diet, reduced sodium intake, reduced body fat influence the pathophysiology at many points of hypertension control.

High sodium intake is strongly correlated with the development of hypertension. It leads to increased intravascular fluid volume and cardiac output, peripheral resistance and higher BP.

It is hypothesized that, in most cases, essential hypertension is a genetic disorder involving many individual genes, each of which influences the body's handling of sodium to varying degrees, and becomes expressed in the context of an unhealthy diet, particularly excessive intake of salt.

Other factors contribute to pathophysiology of hypertension:

A, Stiffening of large conduit arteries in the elderly. Loss of compliance increased systolic BP.

B. Proliferation of smooth-muscle cells and endothelial dysfunction in small vessels causes vasoconstriction and increased peripheral resistance.

C. Although the systemic renin-angiotensin-aldosterone (**R-A-A**) axis is often suppressed in the presence of elevated BP, angiotensin II activity is increased locally in the kidneys, vascular endothelium, and adrenals.

D. Increased activity of the sympathetic nervous system may also be a factor.

E. Both aging and obesity contribute to the pathogenesis of hypertension.

Reduction in salt intake and weight loss are effective in lowering BP. Lowering dietary salt lessens the amount of sodium the kidney has to excrete to restore normal blood volume. Compliance of the large vessels is improved. Activation of the R-A-A system and the sympathetic nervous system are moderated.

Decrease in abdominal visceral fat improves function of both conduit and resistance vessels

CLINICAL EVIDENCE

The most studied and established dietary patterns are:

The Dietary Approaches to Stop Hypertension (DASH[1]) diet was especially effective in patients who had hypertension. When combined with low salt intake, benefit was greater. Benefit of the diet is also accentuated with increasing age.

Sodium reduction, the DASH diet (vs controls), and changes in systolic BP:

Sodium	Controls	DASH
3.5 g daily	143 mm Hg	135 mm Hg
2.3 g	141	133
1.2 g	135	128

(Note the systolic BP of the controls was also lowered by salt restriction.)

A high protein diet (vs a high carbohydrate diet) and a high unsaturated fat diet lowered BP, especially in persons with hypertension.

When weight loss was added to the diets BP was reduced to a greater extent.

CLINICAL USE

Dietary management is appropriate for all patients with hypertension, and for those with pre-hypertension. (Defined as 120-139/80-89)

Use of BP medications should not supplant dietary treatment. The two treatment forms should be considered complimentary, including use in patients resistant to drug therapy who are taking several anti-hypertension agents. (The authors use a healthful diet chart shown in table 1 of the article.)

In simple terms:

Eat poultry, fish, nuts, legumes, low-fat and non-fat dairy, vegetables, fruit, whole grains, poly - unsaturated and mono-unsaturated fats (olive, canola, soybean, peanut, corn, sunflower, safflower oil). Similar to the Mediterranean Diet.

Avoid red meat, full fat dairy, snacks and desserts high in sugars, white flour, butter, coconut oil, palm-kernel oil, sweetened beverages, candies, and cookies . Canned and processed foods should be limited unless their salt content has been eliminated.

Adopting a healthy diet means making choices in the market. *(Table 1 of the article presents a shopping guide.)*

For convenience, low sodium frozen or canned vegetables can be substituted for fresh ones. Patients should become familiar reading food labels Sodium restriction is essential .

Patients should not skip meals, should consume one third of their daily food intake at breakfast, and should limit eating in restaurants.

“We always recommend that patients record their dietary intake for 1 or 2 weeks, and discuss this record with a dietician.”

The costs associated with dietary treatment of hypertension are relatively modest.

AREAS OF UNCERTAINTY

One crucial frontier of dietary research is that of devising and evaluating effective behavioral and community-based interventions. In the DASH trials, dietary modifications were studied over a short time span, and participants were carefully monitored for compliance. “We need to learn what components of behavioral interventions lead to adherence.”

GUIDELINES

"We recommend the American Heart Association guidelines for cardiovascular health and dietary management of hypertension." [2] 1.5 g sodium per day is optimal. These guidelines are similar to the DASH diet. A BMI less than 25 is also recommended. Alcohol intake is limited.

"We also recommend a small consistent daily restriction in calorie intake of 200 to 300 kcal per day, coupled with an increase in physical activity,"

"A trial of intensive dietary treatment is warranted for 6 months to try to achieve the target goal for blood pressure (systolic < 140 and diastolic < 90) before medication is introduced ."

Patients should monitor their BP at home.

NEJM June 2, 2010; 362: 2107-12 "Clinical Therapeutics" first author Frank M Saks, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass.

1 Google will lead to a number of references to the DASH diet

2 Also on Google "American Heart Association Diets"

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Importance Of Maintaining Optimal Weight During Middle Age For Prevention Of Diabetes

6-4 ASSOCIATION BETWEEN ADIPOSITY IN MIDLIFE AND OLDER AGE AND RISK OF DIABETES IN OLDER ADULTS.

Incidence of type-2 diabetes (**DM-2**) is highest among adults 65 to 79 years of age.

About 70% of US men and women older than age 60 are overweight or obese (body mass index 25 and over.)

Changes in body composition occur with aging, including increase in fat mass, loss of muscle mass, redistribution of adipose tissue, and height shrinkage.

This study examined the relationship between measures of overall body fat, body fat distribution, changes in these measures, and risk of DM-2 in older adults.

STUDY

1. The Cardiovascular Health Study is a prospective population-based cohort study of older adults. In 1989-1990, a group of 5201 ambulatory, non-institutionalized men and women age 65 and older (mean = 73) were randomly recruited. A supplemental cohort of 687 African Americans was recruited in 1992-93.
2. After exclusions for diabetes and other reasons, a cohort of 4193 remained.

3. At baseline and periodically thereafter, collected comprehensive information on health-related variables. Self-reported body weight at age 50 was collected at baseline.
4. Clinical examinations were performed periodically from 1989-1990 to 1998-1999, and again in 2006-2007.
5. Periodically determined height, body weight, and waist circumference (**WC**).
6. Calculated body mass index (**BMI**) from the self-reported weight at age 50 and the measured height at baseline. Determined BMI at baseline from measured weight and height.
7. Glucose was measured on fasting serum periodically. Classified participants as having DM-2 if fasting glucose was 126 mg/dL and above.
8. Categorized participants by sex-specific quintiles of BMI.

RESULTS

1. Over a median follow-up of 12 years, 339 new cases of DM-2 occurred among 4193 participants.
2. At baseline (1989-90), 45% of participants had prediabetes (fasting glucose 100 to 125 mg/dL).
3. BMI at baseline, BMI at age 50, and waist circumference were strongly related to risk of developing DM-2
4. Association between baseline measures of adiposity and risk of incident DM-2 in men 1989-2007.:

BMI quintiles	<23.3	23.3 - 25.0	26.1 - 26.6	26.7 - 28.6	>28.6
Hazard ratio (**HR**) for DM-2	1.00	1.9	2.9	4.4	5.6
Waist circumference (cm)	< 89.1	89.1 - 94.0	94.1 - 99.0	99.1 - 104.5	>104.5
HR for DM-2	1.00	2.1	2.2	3.9	5.1

(Ie, men with higher BMI and WC at baseline were much more likely to develop DM-2. Women had similar associations)

5. Participants in the highest category of adiposity had approximately 2- to 6- fold increased risk of developing DM-2 compared with those in the lowest category. The strongest association between waist circumference and risk of DM-2 was driven primarily in participants with a BMI *less* than 25.
6. The mean change in weight from age 50 to study entry was 4.3 g for women and 1.3 kg for men.
7. Risk of developing DM-2 based on BMI at age 50 and changes in weight between age 50 and at age of 73 (mean age at entry into the prospective study):

BMI < 25 at age 50 HR for DM-2

Loss of 2 kg 0.6

Gain or loss of 2 kg 1.0 (Referent)

Gain of 2.1 to 5.9 kg 1.0

Gain of 6 to 8.9 kg 1.3

Gain of 9 kg and over.3.2

BMI >29 at age 50

Loss of 2 kg 2.3

Gain or loss of 2 kg 2.4

Gain of 2.1 to 8.9 kg 3.5

Gain of 9 kg and over. 5.0

(Ie, if BMI was higher at age 50, the risk of developing DM-2 increased. The risk of DM-2 increased monotonically with the amount of weight gained between age 50 and study entry.)

8. Participants in the highest categories of both BMI and waist circumference had more than 4 times the risk than those in the lowest categories of both measures.

DISCUSSION

1. "We found that measures of overall and central adiposity were strongly associated with the risk of incidental diabetes in both men and women."
2. Weight gain during midlife (after age 50) and in late life (after age 65) is an important risk factor for diabetes among older adults.
3. BMI and waist circumference were as strongly associated with risk as were other measures of obesity. (Bioelectric impedance for measurement of fat, waist-hip ratio, waist-height ratio)
4. It is possible that regional fat distribution is more important in the etiology of diabetes than absolute fat mass. Visceral fat and thigh fat are associated with impaired glucose tolerance and diabetes in older adults independent of total adiposity.
5. This analysis showed an association between waist circumference and diabetes risk in individuals with a BMI less than 25, suggesting that measurement of waist circumference may add important information beyond BMI regarding diabetes risk in normal weight individuals.
6. This study affirms the importance of maintaining optimal weight during middle age for prevention of diabetes. "Weight control remains important in reducing diabetes risk among adults 65 years of age and older."

CONCLUSION

Among older adults, overall and central adiposity, and weight gain during middle age and after age 65 were associated with increased risk of diabetes.

JAMA June 23/30 2010; 303: 2504-12 Original investigation, first author Mary L Biggs, University of Washington, Seattle.
Supported in part by the National Heart, Lung, and Blood Institute.

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Less Frequent Tooth Brushing--More Periodontal Disease--Higher Risk of CVD

6-5 TOOTH BRUSHING, INFLAMMATION, AND RISK OF CARDIOVASCULAR DISEASE: RESULTS FROM A SCOTTISH HEALTH STUDY

There has been increasing interest in a possible link between dental disease, specifically periodontal disease (**PD**), and CVD. Inflammation plays an important link in the pathogenesis of atherosclerosis. Markers of low-grade inflammation have been consistently associated with a higher risk of CVD.

Poor oral hygiene is the major cause of PD, a chronic infection of the tissue surrounding the teeth. It is one of the most common chronic infections and is associated with a moderate systemic inflammatory response such as raised concentrations of C-reactive protein and other inflammatory markers.

Systemic inflammation could represent the underlying mechanism linking oral health and CVD. Oral infection might add to the inflammatory burden of the individual, raising levels of C-reactive protein and fibrinogen, resulting in increased levels of risk.

Self-reported measures of oral hygiene have been associated with confirmed periodontal disease.

This study examined whether self-reported tooth brushing behavior is associated with increased markers of inflammation and CVD.

STUDY

1. The Scottish Health Study is a cross sectional survey of a nationally representative sample of the general population living in Scottish households. The study included data from the 1995, 1998, and 2003 surveys in adults age 35 and older.
2. Interviewers visited households and collected data on demographics, medical history, and health behaviors, including oral health. Oral health behavior was assessed from self-reported frequency of visits to a dentist, and tooth brushing (twice daily, once daily and less than once a day.)
3. In a sub-sample of 4830 individuals, collected blood for analysis of C-reactive protein and

fibrinogen. Examined the association between frequency of tooth brushing and these inflammatory markers.

4. Linked the database to hospital admissions and deaths.
5. Primary endpoint = composite of fatal and non-fatal CVD.

RESULTS

1. The final sample size was 11 869.
2. Characteristics of the study population in relation to oral hygiene:

	Frequency of tooth brushing		
	Twice daily (n = 8481)	Once a day (n = 2880)	Rarely/never (n = 538)
Mean age	49	51	51
Male (% of n)	39	61	85
Dental visits (rarely)	16	32	62
Smokers	25	31	48
Obesity	19	27	34
Hypertension	22	28	32
Diabetes	2	3	7

(Participants who had poor oral hygiene habits also had more risk factors for CVD. Scottish men seem to be the chief offenders. RTJ.)

3. There were 555 CVD events over an average of 8 years.
4. Model of tooth brushing and CVD:

Tooth brushing	Hazard ratio (adjusted for multiple possible confounders)\
Twice a day	1.00 (reference)
Once a day	1.3
< Once a day	1.7

5. Participants who reported less frequent tooth brushing had a 70% increase in risk of CVD.
6. There were significant associations between frequency of tooth brushing and markers of low grade inflammation:

	C-reactive protein Mean mg/L	Fibrinogen Mean g/L
Twice a day	3.07	2.86
Once a day	3.51	2.95

< Once a day	4.18	2.98

DISCUSSION

1. “Tooth brushing is associated with cardiovascular disease.”
2. “Our results also suggest that tooth brushing is associated with concentrations of C-reactive protein and fibrinogen.”
3. The role of oral health in the etiology of CVD has received considerable attention. PD is a complex chronic inflammatory disease resulting in loss of connective tissue and bone support to the teeth. It is caused mostly by poor oral hygiene. It is a major cause of tooth loss in adults over age 40. It is highly prevalent, especially in late middle age when coronary artery disease is also most common.
4. In this study, participants who brushed their teeth less often had a 70% increase in risk of CVD events compared with frequent brushers. This confirms findings from several observational epidemiological studies. The NHANES I study (1993) reported that people with periodontal disease had a 25% increased risk for CVD relative to those who had minimal disease.
5. Because nearly 40% of the population has periodontal disease, this modest increase might have a profound public health impact.
6. Less frequent tooth brushing was associated with increased concentrations of both C-reactive protein and fibrinogen. The literature clearly shows that raised pro-inflammatory cytokines are present in both CVD and PD.
7. This study was nationally representative, with a rigorous design and data linked to hospital admissions and deaths. The Scottish population is relatively homogeneous, with a high incidence of CVD and poor indicators of oral health. The findings have relevance in this population.
8. Doctors should be alert to the possible oral source of an increased inflammatory burden. Patients should be educated in improving oral hygiene regardless of the relation with systemic disease

BMJ 2010;340:c2451 doi:10.1136/bmj.c2451

A short version of this study was presented in BMJ June 26, 2010;340:1400 First author Cesar de Oliveira, University College, London

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Oseltamivir Ring Chemoprophylaxis Was Effective In Reducing an Outbreak of 2009 H1N1 Flu

6-6 OSELTAMIVIR RING PROPHYLAXIS FOR CONTAINMENT OF 2009 H1N1 INFLUENZA OUTBREAKS.

This study describes the Singapore experience in responding to 4 outbreaks of 2009 pandemic influenza A (H1N1) virus in military camps and evaluates the role of oseltamivir "ring chemoprophylaxis" in attenuating transmission of the virus.

STUDY

1. All Singapore men perform 2 years of military service after high school. Most live in barracks on weekdays and return home weekends. There is interaction between the military and the general population.
2. The first case of H1N1 occurred on May 27, 2009. The first transmission to the community was reported June 18, 2009.
3. A suspected case of influenza was defined as influenza-like illness (temperature 38^{o} or more, with cough or sore throat) with onset of symptoms within 7 days after travel to an affected area, close contact with a person with confirmed infection, or contact with a local cluster of infected persons. Prompt laboratory confirmation was by polymerase-chain-reaction.
4. Persons with confirmed infection were isolated in hospitals.
5, Contacts were defined as persons who had unprotected exposure to an infected person since the day before to onset of symptoms. Most contacts were quarantined at home for 7 days.
6. The Singapore Armed Forces implemented additional interventions to contain the spread of flu, primarily "ring prophylaxis" with oseltamivir (*Tamiflu*, Roche) 75 mg orally daily. A 10-day course of *Tamiflu* was administered to coworkers for 10 days after exposure to an infected person. (Coworker defined as a member of the same military unit where contact opportunities were substantial. Larger prophylaxis rings were instituted if cases were present in multiple units.
7. All personnel with suspected infection were tested with PCR within 24 hours, and isolated if the test was positive. All symptomatic persons in the same unit were screened through collection of nasopharyngeal swabs 3 times a week to detect subclinical infection.

RESULTS

1. Summary of 4 outbreaks:

Total number of personnel	1175
Confirmed cases	82 (7%)

Before intervention 75 (6.4%)

After intervention 7 (0.6%)

(After prophylaxis began, in combination with home leave to avoid contacts, only 7 more cases were confirmed.)

2. 95% completed oseltamivir prophylaxis.
3. All 7 cases with onset after prophylaxis occurred within 4 days after the intervention.
4. The authors used a mathematical model to investigate the effects of interventions. If only confirmed cases were considered, the global estimate of the reproductive number before intervention was 1.9. After intervention--0.11.
5. Adverse effects of oseltamivir: 8% reported mild, non-respiratory symptoms. There were no neuropsychiatric events; no severe adverse events reported.

DISCUSSION

1. Influenza outbreaks can be rapid and severe in semi-closed and closed environments. In a Taiwanese outbreak among military recruits, 58% were infected. On a US navy ship infection rate was 42%. Infection rates can be high in schools. In this study, during outbreak 4, 59 cases occurred within 4 days after the first contact.
2. Two modeling studies have predicted the effectiveness of ring prophylaxis. The use of post exposure prophylaxis with oseltamivir in close household contacts resulted in protective efficacies of 68% and 89%.
3. "In the present study, we have shown that ring prophylaxis with oseltamivir, given after exposure in military camps, was effective, allowing training and operations to continue while substantially reducing the risk of further generations of cases during prophylaxis."
4. The study reflects the limitations of quarantining only people considered to be close contacts of an affected person.
5. Ring prophylaxis based on spatial proximity was more effective in controlling the spread of disease than was the focus on close contacts.
6. Antiviral prophylaxis may be considered as an additional strategy to vaccine in reducing pandemic effects.
7. People do endeavor to spontaneously distance themselves socially during an epidemic.
8. The use of oseltamivir prophylaxis as a containment measure may be limited to semi-closed or closed communities.
9. Early case detection and use of antiviral ring prophylaxis effectively truncated the spread of

infection during an epidemic. Aggressive prophylaxis may be justifiable to protect vulnerable populations such as frail or elderly residents of long-term care facilities, or persons in closed communities.

CONCUSSION

Oseltamivir ring chemoprophylaxis, together with prompt identification and isolation of infected personnel, was effective in reducing the impact of the outbreak of 2009 H1N1 influenza in semi-closed settings.

NEJM June 10, 2010; 362;2166-74 Original investigation, first author Vernon J Lee, Biodefence Centre, Ministry of Defense, Singapore

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