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SEPTEMBER 2011

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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 **FULL 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* SEPTEMBER 2011

Creation Of An Increase In Public Consciousness And A Catalyst For Change

9-1 UN MEETING FOR NON-COMMUNICABLE DISEASES

On 19-20 September 2011, the United Nations General Assembly hosted a meeting on control and prevention of non-communicable diseases (NCD)—specifically diabetes, lung disease, cardiovascular disease (CVD), and cancer—the diseases that “break the bank”. CVD was high on the agenda.

Thirty world leaders and 100 senior ministers signed a policy agreement to tackle the world’s major health problems.

Health ministers from low and middle-income countries were the major catalysts for the meeting.

Months of hard work and tense negotiations preceded the meeting. Much evidence had been amassed in the run up to the summit.

Although the meeting was held in New York City, the eyes of developing country leaders, decision makers, civil society groups, industry, non-government organizations, and researchers focused on the event and its outcome.

The meeting offered a unique opportunity to review and set priorities, share best practice, and coordinate global priorities. It put NCD firmly on the global agenda.

Modest population-wide behavioral changes can produce large benefits and can be highly cost-effective. Previous UN summits have provided a catalyst for improvement in health.

The UN meeting was a crucial moment, especially because it developed in the shadow of global efforts to achieve the millennium development goals, which did not include NCD.

NCDs are by far the largest killers on the planet—the cause of 63% of the deaths. They receive less than 3% of international development assistance for health.

About 80% of ncd deaths occur in developing countries, generally in younger populations than in higher income countries. The WHO predicts a 17% global increase in ncd deaths over the next 10 years, especially in African, Eastern Mediterranean, Western Pacific and South East Asia countries.

Whatever happens after the meeting, it has led to the creation of an increase in public consciousness about ncd. What has emerged from the meeting is that a “whole of government and whole of society” approach is needed to tackle ncd.

Eight dietary targets for prevention of cardiovascular disease (CVD):

Fruits

Vegetables

Whole grains

Nuts

Vegetable oils

Sea food

Sodium limitation

Trans fat elimination

Meeting any one target would produce substantial benefits. Meeting all targets could halve global CVD and prevent over 5 million premature deaths annually, while simultaneously reducing obesity, diabetes, and common cancers.

Other suggested interventions: (With the help of governments)

Subsidize healthy food and drink.

Tax less healthy foods.

Promote the infrastructure for production, transportation, and marketing of healthy foods.

Limit salt and trans fat distribution.

Provide strict guidelines to limit distribution of harmful food and drink to children.

Focus media and educational campaigns on healthy foods.

Mandate product and menu labeling.

Make healthy foods available in disadvantaged neighborhoods.

Incorporate healthy foods in the workplace and in schools.

Incorporate dietary curriculums and training for teachers and students in schools.

Drug based preventive approaches that target those at high risk can be costly and unsustainable in many countries.

BMJ September 17, 2011; 343: 546-47 Editorial, first author Dariush Mozaffarian, Brigham and Women's Hospital and Harvard Medical School, Boston, Mass.

Note: This communication was written before the meeting. I translated it into past tense. Ed.

BMJ September 26, 2011 presented further comment by Fiona Godlee Rebecca Coombes, and Tom Delamothe

The ultimate goal of health interventions is to prolong an independent and productive life, and to shorten the period of disability and dependence.

Major efforts to extend a completely dependent and demented life (vs compassionate supportive care) can be counter-productive.

The articles focused on lifestyles, mainly on healthy foods for prevention of CVD. Less attention was paid to tobacco and alcohol.

This effort, I believe, is the beginning of the beginning of a long international intervention. Government interventions may be helpful to some extent, but the major benefits will come from educating of the public, starting in childhood. Changes made willingly from the bottom up will be more effective and lasting than changes mandated from the top down.

There are massive barriers to overcome. Change will come very slowly.

Culture, poverty, costs, and, ingrained habits will impede progress. Powerful commercial interests (tobacco, alcohol, meat production, dairy) and political groups stand in the way. (Note the present uproar denouncing government interference with private life.) Nevertheless, some progress has been made in the US. New York City has been successful in limiting trans fats. Tobacco taxation and education have reduced prevalence of use, Efforts to lower availability of unhealthy food and drink in schools have progressed. But, alcohol and illicit drug use seem to proceed unabated.

Some individuals believe that drinking alcohol, smoking and imbibing sugary soft drinks are expressions of freedom.

I believe the major effort, by far, to improve length of healthy life depends on education. Primary care clinicians can play a major role in education. Changing to a healthy lifestyle will benefit more than preventive drugs.

Superior To Warfarin In Preventing Stroke, Caused Less Bleeding And Lowered Mortality

9-2 APIXABAN VERSUS WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION

The ARISTOTLE Study

Vitamin K antagonists are highly effective in preventing stroke in patients with atrial fibrillation (AF). But they have limitations. Many patients who would benefit from warfarin do not receive it.

Apixaban is a novel oral direct factor Xa inhibitor that has been shown to reduce risk of stroke in comparison with aspirin in patients with AF.

This randomized, double blind trial (n = 18 201; median age 70) compared apixaban (5 mg twice daily) with warfarin (target INR 2.0 to 3.0) in patients with AF and at least one additional risk factor for stroke (age > 74; previous stroke; TIA; systemic embolism; symptomatic heart failure; diabetes; or hypertension).

Primary outcome = ischemic or hemorrhagic stroke or systemic embolism. The trial was designed to test for non-inferiority.

The median duration of follow-up was 1.8 years.

Rates per year (%)	Apixaban	Warfarin	HR*	RR **	NNT***	Benefit 1000/y****
Primary outcome	1.27	1.60	0.79	0.33	300	3
Major bleeding	2.13	3.09	0.69	0.96	100	10
Death from any cause	3.52	3.94	0.89	0.42	230	5
Hemorrhagic stroke	0.24	0.47	0.51	0.23	425	3

(* Hazard Ratio ** % Risk Reduction)

(***Number needed to treat to benefit one ****Benefit per 1000 patients per year. *(My calculation [approximate] Ed.)*

For every 1000 patients treated for 1.8 years, apixaban compared with warfarin prevented stroke in 6, major bleeding in 15, and death in 8.

The rate of discontinuation was lower in the apixaban group.

The predominant effect on stroke prevention was on hemorrhagic stroke (4 patients per 1000).

Ischemic stroke was prevented in 2 per 1000.

Conclusion: In patients with AF, apixaban was superior to warfarin on preventing stroke or systemic embolism, caused less bleeding, and resulted in lower mortality.

NEJM September 15, 2011; 365; 981-92 Original investigation by the ARISTOTLE committee and investigators, first author Christopher B Granger, Duke University Medical Center, Durham NC.

ARISTOTLE “Apixaban Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation” Study supported by Bristol-Myers-Squibb doi 10.1056/NEJMoa1107039

Apixaban: Trade name Eliquis—Pfizer and Bristol-Myers-Squibb

Past studies have reported that apixaban is equivalent or superior to the low-molecular-weight heparin enoxaparin in preventing thrombosis in patients undergoing knee and hip replacement. And it is much superior to aspirin in preventing stroke in patients with AF.

In another study in patients after an acute coronary syndrome, apixaban increased the rate of bleeding without significant reduction in recurrent ischemic events.

Source: Wikipedia

Non-Inferior To Warfarin For Prevention Of Stroke. No Significant Difference In Risk Of Major Bleeding.

9-3 RIVAROXABAN VERSUS WARFARIN IN NON-VALVULAR ATRIAL FIBRILLATION: The ROCKET AF Trial

Rivaroxaban is a novel factor Xa inhibitor.

This double-blind multinational trial randomized 14 264 patients (Median age 73) with non-valvular AF. All were at moderately-high increased risk for stroke because of a history of stroke or TIA, or two of the following—heart failure; left ventricular ejection fraction < 35%; hypertension; age > 74; diabetes.

Randomized to: 1) rivaroxaban (20 mg once daily) or 2) warfarin (dose adjusted to target INR 2.0 to 3.0).

Primary endpoint = stroke or systemic embolism.

Per protocol*	Rivaroxaban	Warfarin	HR	RR***	NNT ***	Benefit/1000****
Primary endpoint (%/y)	1.7	2.2	0.79	0.5	200	5
Intention-to-treat analysis						
Primary endpoint (%/y)	2.1	2.4	0.80	0.3	333	3
Bleeding***** %/y	14.8	14.5	-	-	-	-
Intracranial hemorrhage	0.5	0.7	71	0.2	500	2
Fatal bleeding	0.2	0.5	0.40	0.3	333	3

(* Those who completed the trial. ** % risk reduction. ***Number needed to treat to benefit one patient.****Benefit for every1000 patients treated for one year.***** Major or clinically significant bleeding)

In both the intention-to-treat (included all randomized) and the per-protocol analyses (those that actually completed the trial) rivaroxaban was non-inferior to warfarin in prevention of stroke and systemic embolism. Although an intention-to-treat analysis is the standard method for assessing superiority, non-inferiority is best established when patients are actually taking the randomized treatment.

In the primary safety analysis, there was no significant difference with respect to bleeding. Fatal bleeding and hemorrhagic stroke occurred less frequently with rivaroxaban. Gastrointestinal bleeding was more common with rivaroxaban as well as bleeding that resulted in a drop in hemoglobin of 2 g/dL, or required a transfusion.

Among those taking warfarin, the proportion of time in which the INR was within the therapeutic range was 55%.

Conclusion: Rivaroxaban was non-inferior to warfarin for prevention of stroke and systemic embolism. There was no significant difference in risk of major bleeding. Intracranial and fatal bleeding were less common in the rivaroxaban group

NEJM September 8, 2011; 365: 883-91 doi: 10.1056/NEJMoa1009638

Original investigation by the ROCKET AF investigators “Rivaroxaban Once Daily Oral Direct Factor Xa Inhibitor Compared with Vitamin K Antagonists for Prevention of Stroke and Embolism Trial in Atrial Fibrillation” first author Manesh R Patel, Duke University Medical Center, Durham, NC

Rivaroxaban – trade name Xalto by Bayer and Janssen.

Rivaroxaban is the first available oral active direct factor Xa inhibitor. It is highly selective. It does not affect thrombin or platelet activity.

There is no need for dose adjustment or routine coagulation monitoring.

Maximum inhibition occurs within 4 hours. Activity does not return to normal within 24 hours.

Once-a-day dosing is possible. The daily dose in various studies has varied.

Rivaroxaban is non-inferior to 40 / d mg subcutaneous enoxaparin in preventing venous thrombo-embolism (VTE) in patients undergoing hip and knee replacement. Another study found that it was more effective than enoxaparin. However, risk of bleeding is greater.

It has been approved by the FDA for prevention of VTE in patients undergoing hip and knee replacement.

In acutely ill medical patients, rivaroxaban taken for 35 days was reported to be superior to 10 days of enoxaparin in preventing VTE, but bleeding was greater.

There is a question of rare occurrence of live toxicity.

Action cannot be readily reversed.

It should be avoided in patients with severe renal impairment and with caution in patients with moderate renal impairment.

Drugs that affect the CYP3A enzyme may significantly affect rivaroxaban exposure.

NSAIDs, aspirin, or clopidogril used with rivaroxaban may increase bleeding.

Source: Wikipedia

Associated With Lower Rates Of Stroke, With Similar Rates Of Bleeding

9-4 DABIGATRAN VERSUS WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION THE RE-LY STUDY

(This study was published in NEJM September 2009. I abstract it now to compare with the previous 2 studied. Ed.)

Dabigatran is a new oral direct thrombin inhibitor.

This multicountry study (2008-09) randomized 12 098 patients with AF (mean age 71) to fixed doses of dabigatran (150 mg twice daily) vs warfarin titrated to INR 2.0 to 3.0 (Twice daily administration reduces the variability in the anticoagulant effect.)

Concomitant use of aspirin was permitted. It was used continuously in 20% of dabigatran patients and 21% of warfarin patients.

All patients were at increased risk of stroke, similar to the previous two studies.

Primary outcome = stroke or systemic embolism. Primary safety outcome = major hemorrhage..

The primary analysis was designed to test whether dabigatran was non-inferior to warfarin. Analysis was by intention-to-treat.

Follow-up was for 2 years.

RESULTS

	Dabigatran	Warfarin	HR	RR%	NNT*	Benefit / 1000*
Primary outcome %/ y	1.11	1.69	0.66	0.58	172	6
Major bleeding %/y	3.11	3.36	0.93	0.25	400	2.5
Hemorrhagic stroke %/y	0.10	0.38	0.26	0.28	357	3
Death from any cause %/y	3.64	4.13	0.88	0.49	212	5

Dabigatran was statistically superior to warfarin for the primary outcome of stroke and systemic embolism.

The risk of major bleeding was similar between groups.

Dabigatran reduced the rates of hemorrhagic stroke and death from any cause.

The risk of myocardial infarction was actually higher in the dabigatran group vs warfarin (0.74% vs 0.53%. Relative risk = 1.38)

There was a significantly higher risk of major gastrointestinal bleeding in the dabigatran group.

Twenty one % of dabigatran patients discontinued treatment vs 17% for warfarin.

DISCUSSION

The 150 mg dose of dabigatran was statically superior to warfarin with respect to the primary outcome of stroke and systemic embolism. And was non-inferior with respect to major bleeding.

Warfarin reduces risk of myocardial infarction (**MI**). The lower rate of MI with warfarin might be due to warfarin's greater effect on coagulation factors (II, VII, IX, C and S). Dabigatran is selective for thrombin.

The rate of hemorrhagic stroke with dabigatran was less than 1/3 the rate with warfarin. This, with a greater reduction in rate of ischemic stroke, suggests an important advantage of dabigatran.

The increased rate of gi bleeding, despite a lower overall rate of bleeding from dabigatran may have been due to the tartaric acid component of the dabigatran capsules.

Dyspepsia was the only significant adverse effect of dabigatran.

There was no evidence of liver damage, or increase in creatinine clearance.

Conclusion: Compared with warfarin, 150 mg dabigatran twice daily was associated with lower rates of stroke, with similar rates of bleeding.

NEJM September 17, 2009; 361: 1139-51 Original investigation by the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) investigators, first author Stuart J Connolly, McMaster University, Hamilton, Ontario, Canada Study doi 10.1056/NEJMoa090556

Dabigatran is marketed as Pradaxa by Boehringer Ingelheim.

The study also reported a similar number of patients treated with 110 mg twice daily. I omit this data. The FDA has not yet approved this dose because the 150 mg dose was superior to warfarin in prevention of stroke while the 110 mg dose was non-inferior.

Aspirin may have distorted the results because aspirin may have different effects on the harms and benefits of both drugs. The study would have been more straightforward if aspirin had not been used so frequently in both the warfarin and dabigatran groups. Indeed, concomitant use of other anticoagulants (aspirin, NSAIDS, and clopidogril) are strongly discouraged.

Although the NNT in favor of dabigatran is high, the population benefit may be great because anticoagulants are used so frequently. The lower incidence of hemorrhagic stroke is also a big plus.

Dabigatran was associated with a greater risk of myocardial infarction. Thus far, I have encountered no studies showing benefit from the newer anticoagulants in treatment in acute coronary syndromes.

There is some suspicion that fatty foods and proton-pump inhibitors may delay absorption.

A study in NEJM December 2009 reported that dabigatran was as effective as warfarin in treatment of venous thromboembolism. doi 10.1056/NEJMoa0906598

EDITORIAL COMMENTS ON THE ANTICOAGULANT STUDIES:

I believe these drugs represent a major therapeutic advance.

The fixed daily dose, and lack of the need for monitoring the dose will increase convenience and compliance. (Many patients who would benefit from anticoagulation do not receive it now because of the requirement for frequent monitoring the dose of warfarin.)

Use in prevention and treatment of venous thromboembolism will increase.

The lower risk of hemorrhagic stroke is a big plus.

Optimum doses must be determined.

We still do not know the whole story about interaction with other drugs and foods. And possible adverse effects on the liver and the risks of use in patients with renal disease.

We need to know the rapidity of onset and offset of action for each drug.

There is no antidote to quickly reverse the effects of excessive bleeding. Or to lower risk of bleeding in trauma patients and those requiring emergency surgery.

Thus far, no benefit has been shown for acute coronary syndromes.

All are costly.

The benefit / harm-cost ratio must be assessed for each drug. All have strengths and weaknesses. There is likely to be a lively debate as to which drug is best. Is there a "best" drug? (Watch out for "spin". Thus far, dabigatran has the advantage of a longer period of observation. Will head-to-head comparisons become available?

Other oral anticoagulants are on the way.

Should primary care clinicians now begin to use these drugs? I believe prudence is needed.

We need more time to determine safety, dosage, adverse events, and drug interactions. They certainly look promising.

There is no need to switch to a newer drug if the patient is doing well on warfarin.

Physicians Need To Be Selective, Cautious, And Vigilant

9-5 LONG-TERM OPIOID THERAPY RECONSIDERED

For 2 decades, opioid therapy for chronic non-cancer pain has been contentious and controversial. Now, two points are widely agreed on:

- 1) Chronic pain has substantial negative effects. About 25% of adults have moderate to severe chronic pain. About 10% have disabling chronic pain that limits work and family activities. Patients who seek medical care for chronic pain deserve compassionate care and evidence-based management.

2) The increase in prescribing opioids for chronic non-cancer pain has been accompanied by alarming increases in opioid misuse and abuse, and fatal overdoses due to illicit diversion of prescription opioids. This situation is urgent, resulting in recent calls for action by the federal government.

Debate about long-term opioid therapy (**LTOT**) seems to pit commitment to compassionate care against adequate response to an epidemic of opioid abuse and overdose. These goals need not be mutually exclusive.

Effectiveness of LTOT: Studies of LTOT versus alternative treatments are few and suggest limited advantages for opioids. A 2009 evaluation of evidence for LTOT by the American Pain Society rated 21 of 25 of their recommendations as based on “low quality evidence”. A recent survey of primary care patients receiving LTOT found that most patients continued to report moderate to severe pain and that functional outcomes are often poor.

Nonetheless, clinicians report that some patients with chronic pain seem to experience meaningful benefit, reflecting patients’ variability in response to LTOT.

Risks of LTOT: Consistent estimates of the prevalence of opioid abuse among primary care patients receiving LTOT remain elusive. The few surveys in community practice estimate rates of abuse from 4% to 26%. Recent surveys suggest that potentially serious abuse is not rare. A survey of 800 persons receiving LTOT found purposeful overuse in 26%; 39% increased dose without prescription; 8% obtaining opioids from other doctors; 18% used drugs for purposes other than pain; 20% drank alcohol to relieve pain; and 12% hoarded drugs. Use of diverted prescription opioids is now among the most common forms of drug abuse, with the risk of addiction and fatalities.

Decisions about prescribing need to take into account the risks to family and community in addition to direct risks for the patient.

Other risks of LTOT include serious fractures, breathing problems during sleep, depression, immunosuppression, chronic constipation, bowel obstruction, myocardial infarction, and tooth decay due to xerostomia.

Nonetheless, recent guidelines from the American Geriatric Society concluded that all patients with moderate to severe pain be considered for opioid therapy. This recommendation was based in part on the unfavorable safety profile of NSAIDs for managing chronic pain in older adults.

However, a subsequent meta-analysis concluded that the safety of LTOT in elderly patients was not yet established.

The authors of this article conclude that risks of LTOT have not been adequately studied, although recent research has identified important risks.

Safe prescribing: Guidelines advocate management of LTOT by a single physician, clinical risk evaluation, treatment agreements, urine drug screening, periodic monitoring, and documentation of treatment in the medical record.

Safe prescribing of LTOT now depends on decisions by the individual physician. Practical steps to reduce harms include more careful patient selection, increased caution in dose escalation, and close monitoring. Clinicians should taper and discontinue therapy for those who do not benefit or who seriously misuse the drugs.

Increased selectivity before and after initiation of LTOT and greater care in dose escalation could increase safety. This would limit the amount of opioids in the community and decrease the opportunity for diversion.

Physicians need to be selective, cautious, and vigilant when considering LTOT.

(For details see the Full Abstract Ed.)

This article stresses non-cancer pain. While abstracting it, I wondered if there were any differences in treatment of cancer pain. I believe so, for at least two reasons: 1) Clinicians can judge the severity of cancer pain more accurately than non-cancer pain. And can feel more secure in prescribing LTOT. 2) The duration of LTOT is likely to be limited by the cancer.

This study is based on expert opinion and experience. Opinions are conflicting. We really do not know much about risks and benefits of treating an individual. Guidelines are not very helpful.

The article suggests that treatment of chronic pain deserves evidence-based management. But there is no evidence base.

If I had to choose between relieving my patient's pain and risk of diversion and harm to the community, I would act on the benefit to my patient, while being alert to the adverse effects to the patient.

The key to approach of safe LTOT therapy is "know your patient". Do you trust her judgment? Is she a responsible person? How does she respond to a trial of opioids? Does she have a supportive and responsible family to oversee therapy?

What are the chances of diversion? What are the risks of her going on to abuse of the drug and addiction? Does addiction alone always contraindicate therapy?

Combined, 5 Low-Risk Lifestyles Reduced Incidence Of New-Onset Diabetes By 72%

9-6 LIFESTYLE FACTORS AND RISK FOR NEW-ONSET DIABETES:

In 2010, 11.3% of the US population had diabetes. Prevalence was 26.9% in those over age 65.

This study examined how combinations of lifestyle factors related to long-term risk of incident type-2 diabetes (**DM-2**). in a large prospective cohort of adults age 50 to 71.

Examined a cohort of 566 401 adults age 50-71 in 1995-96 from 6 states. All participants completed a survey, which included demographic information and a 124-item food frequency questionnaire. After exclusions, 207 479 participants remained (114 996 male; 92 483 female).

Optimal low-risk-lifestyle factors were defined and assessed at baseline:

- 1) Diet: Classified as low risk based on a dietary score. Scores were summarized into quintiles on the basis of intake of low-glycemic index foods, higher ratio of poly-unsaturated fats to saturated fats, higher fiber intake, and low trans fat.
- 2) Alcohol: Moderate intake up to 30g/d for men and 15 g/d for women.
- 3) BMI; 18.5 to 24.9
- 4) Smoking: Never, or discontinued over 10 years ago.
- 5) Physical activity: Participation in at least 20 minutes of activity at least 3 times weekly.

Determined new onset DM-2, self-reported.

Follow-up = 11 years.

Adjusted odds ratios (**OR**) for DM-2 by lifestyle risk factors:

	OR for DM-2	% lower risk
BMI		
18.5-24.9	0.30	70
25 and above	1.00 (reference)	
Diet score		
Top 2 quintiles	0.85	15
Bottom 3	1.00	
Smoking		
Never	0.76	24
Current	1.00	
Moderate alcohol		
Yes	0.81	19
No	1.00	
Physical activity		

Yes	0.76	24
No	1.00	

A strong inverse dose-response relation was observed between number of lifestyle factors in the low-risk category and odds ratios of DM-2. Compared with adults with no lifestyle factors in the low-risk category, and excluding BMI, the ORs for men with 1,2,3 or 4 low-risk factors, were 0.79, 0.66, 0.56, and 0.45.

When family history of DM-2 was factored in, there was no increase in risk of DM-2.

Adiposity was the strongest risk factor for DM-2. However, even after adjusting for adiposity, regular physical activity, a healthy diet, not smoking, and moderate alcohol intake predicted a lower risk. This suggests that these factors affect the risk for DM-2 independently of the effects of adiposity.

A 19% lower risk for DM-2 was observed among men who consumed alcohol moderately compared with those who were abstainers. Women had a 37% lower risk.

Overweight and obese adults may benefit by adopting the remaining low-risk lifestyle factors.

Many persons mistakenly believe that development of DM-2 is inevitable owing to their family history of DM-2. This study did not confirm this belief. Similar results were found among those with and without a family history.

Conclusion: A low risk profile composed of 5 lifestyle factors was strongly associated with a lower risk of new-onset DM-2 among older adults. This has major implications for public health.

(For details and the citation see the Full Abstract Ed.)

Although not surprising, this represents a major intervention for public health. Primary preventions of DM-2 is a major goal of primary care.

Low alcohol intake remains a factor for reducing risk. But, intake must be limited to modest levels daily (the French habit). The same amount of alcohol consumed on week-ends (the Irish habit) increases risk of cardiovascular disease.

Classically, the family history included a question about diabetes. Is this still a valid question?

FULL ABSTRACTS SEPTEMBER 2011

Physicians Need To Be Selective, Cautious, And Vigilant

9-5 LONG-TERM OPIOID THERAPY RECONSIDERED

For 2 decades, opioid therapy for chronic non-cancer pain has been contentious and controversial.

Now, two points are widely agreed on:

- 1) Chronic pain has substantial negative effects. About 25% of adults have moderate to severe chronic pain. About 10% have disabling chronic pain that limits work and family activities. Patients who seek medical care for chronic pain deserve compassionate care and evidence-based management.
- 2) The increase in prescribing opioids for chronic non-cancer pain has been accompanied by alarming increases in opioid misuse and abuse, fatal overdoses, and illicit diversion of prescription opioids. This situation is urgent, resulting in recent calls for action by the federal government.

Debate about long-term opioid therapy (**LTOT**) seems to pit commitment to compassionate care against adequate response to an epidemic of opioid abuse and overdose. These goals need not be mutually exclusive. Clinicians and professional societies can take action now to increase the margin of safety while preserving access to LTOT for carefully selected and closely monitored patients.

Effectiveness of LTOT:

Perceptions that LTOT typically yields long-lasting benefit for patients with chronic non-cancer pain are not supported by strong evidence. Controlled trials lasting 1 to 6 months suggest modest pain relief relative to placebo. No long-term studies have determined whether analgesic efficacy is maintained.

Studies of LTOT versus alternative treatments are few and suggest limited advantages for opioids. A 2009 evaluation of evidence for LTOT by the American Pain Society rated 21 of 25 of their recommendations as based on “low quality evidence”. A recent survey of primary care patients receiving LTOT found that most patients continued to report moderate to severe pain and that functional outcomes are often poor.

Nonetheless, clinicians report that some patients with chronic pain seem to experience meaningful benefit, reflecting patients’ variability in response to LTOT.

Risks of LTOT :

In 1996, the American Pain Society issued a statement supporting use of LTOT. The statement acknowledged the dangers of imprudent prescribing, but concluded that the risk for addiction was low,

and respiratory depression induced by opioids was short-lived, tolerance was not a common problem, and efforts to control diversion should not constrain prescribing.

Unfortunately, experience regarding the risks for addiction, misuse, and overdose in community practice have failed to confirm these assertions.

Consistent estimates of the prevalence of opioid abuse among primary care patients receiving LTOT remain elusive. The few surveys in community practice estimate rates of abuse from 4% to 26%. Recent surveys suggest that potentially serious abuse is not rare. A survey of 800 persons receiving LTOT found purposeful overuse in 26%; 39% increased dose without prescription; 8% obtaining opioids from other doctors; 18% used drugs for purposes other than pain; 20% drank alcohol to relieve pain; and 12% hoarded drugs.

Widespread LTOT leads to greater opioid availability in homes and communities, with adverse public health consequences. Fatal overdose has increased sharply over the past decade--currently over 13 000 deaths per year involve overdose of prescription opioids. Use of diverted prescription opioids is now among the most common forms of drug abuse, with the risk of addiction and fatalities.

Decisions about prescribing need to take into account the risks to family and community in addition to direct risks for the patient.

Other risks of LTOT include serious fractures, breathing problems during sleep, depression, immunosuppression, chronic constipation, bowel obstruction, myocardial infarction, and tooth decay due to xerostomia.

Nonetheless, recent guidelines from the American Geriatric Society concluded that all patients with moderate to severe pain be considered for opioid therapy. This recommendation was based in part on the unfavorable safety profile of NSAIDs for managing chronic pain in older adults.

However, a subsequent meta-analysis concluded that the safety of LTOT in elderly patients was not yet established.

The authors of this article conclude that risks of LTOT have not been adequately studied, although recent research has identified important risks.

Safe prescribing:

Guidelines advocate management of LTOT by a single physician, clinical risk evaluation, treatment agreements, urine drug screening, periodic monitoring, and documentation of treatment in the medical record.

Safe prescribing of LTOT now depends on decisions by the individual physician. Practical steps to reduce harms include more careful patient selection, increased caution in dose escalation, and close

monitoring. Clinicians should taper and discontinue therapy for those who do not benefit or who seriously misuse the drugs.

Increased selectivity before and after initiation of LTOT and greater care in dose escalation could increase safety. This would limit the amount of opioids in the community and decrease the opportunity for diversion. Increased caution with higher doses could reduce diversion.

Balancing the benefits and harms of LTOT:

Physicians for Responsible Opioid Prescribing (**PROP**) developed educational material for clinicians written by experts on LTOT from general medicine, pain medicine, and addiction medicine.

Acute pain management:

Do: Explain that opioids are for time-limited use.

Limit the prescription to the expected time of pain management.

Do not: Prescribe extended-release opioids for acute pain or for opioid-naïve patients.

Chronic pain management:

Do: Talk with the patient about therapeutic goals, risks, and benefits. Prescribe ground rules.

Screen the patient for depression, and other psychiatric disorders, and for substance-abuse history. Realize that patients are reluctant to disclose abuse history.

Explain that discontinuation may be difficult.

Do not: Initiate before considering safer alternatives.

Continue therapy in patients who show no progress toward treatment goals such as increased function and reduced pain.

Assume that the patient knows how to use the drug safely.

Assume that the patient will use the drugs as you intend.

Start long-term therapy if you are not prepared to stop if benefit is not achieved, or if problems arise.

Abandon patients with a prescription drug problem.

PROP advocates acute pain management that reduces the chance of unplanned transition to long-term use. For chronic users, they advocate strategies acknowledging that long-term therapy entails medical, psychological, and addiction risks. Although it is not known whether such guidance will mitigate risks, it reflects steps that clinicians can take to err on the side of caution.

Physicians need to be selective, cautious, and vigilant when considering LTOT.

Combined, 5 Low-Risk Lifestyles Reduced Incidence Of New-Onset Diabetes By 72%

9-6 LIFESTYLE FACTORS AND RISK FOR NEW-ONSET DIABETES:

A Population-Based cohort study

In 2010, 11.3% of the US population had diabetes. Prevalence was 26.9% in those over age 65.

Pharmacological management of diabetes (**DM-2**) has provided benefits, but it is costly and entails adverse effects. It may not be as effective as lifestyle interventions.

Regular physical activity, maintaining optimal body weight, healthy diet, avoidance of smoking, and moderate alcohol intake are associated with lower risk of DM-2. An overall healthy lifestyle that incorporates more than 1 of these factors may be more effective in lowering risk than any single factor.

This study examined how combinations of lifestyle factors related to long-term risk of incident DM-2 in a large prospective cohort of adults age 50 to 71.

STUDY

1. Examined a cohort of 566 401 adults age 50-71 in 1995-96 from 6 states. All participants completed a survey, which included demographic information and a 124-item food frequency questionnaire.
2. After exclusions, 207 479 participants remained (114 996 male; 92 483 female).
3. Optimal low-risk-lifestyle factors were defined and assessed at baseline:
 - Diet: Classified as low risk based on a dietary score. Scores were summarized into quintiles on the basis of intake of low-glycemic index foods, higher ratio of poly-unsaturated fats to saturated fats, higher fiber intake, and low trans fat.
 - Alcohol: Moderate intake up to 30g/d for men and 15 g/d for women.
 - BMI; 18.5 to 24.9
 - Smoking: Never, or discontinued over 10 years ago.
 - Physical activity: Participation in at least 20 minutes of activity at least 3 times weekly.
4. Determined new onset DM-2, self-reported.
5. Follow-up = 11 years.

RESULTS

1. About 50% of the remaining cohort were college graduates, 87% were married, 30% had 2 low-risk lifestyles. They were more likely to consume low total-caloric intake, and to consume more fruits and vegetables.¹

2. Participant characteristics by number of low-risk lifestyle factors. (Means for men):

	0	1	2	3	4	5.
Mean age	62					62
Number	4722					4628
BMI	29	29	28	26	25	23
Never smoked %	0	28	35	40	43	44
Alcohol (g/d)	1.8	1.8	3.3	6.5	10.1	13.9
kcal/d	2200	2100	2100	2000	1900	1900
Fruit (cups/d)	0.7	1.0	1.2	1.5	1.8	1.9
Vegetables cups/ 1000kcal	1.5	1.6	1.8	2.0	2.2	2.3
Total fat g/1000 kcal	38	37	35	33	30	28
Sat. fat g/1000 kcal	13	12	11	10	9	8
Poly/Sat. fat ratio	0.65	0.67	0.73	0.80	0.86	0.91
Trans fat g/1000 kcal	2.7	2.7	2.5	2.2	1.9	1.9
Glycemic index	58	55	54	53	53	52
Fiber g/1000 kcal	8	9	10	11	13	13

3. Identified 17 900 new-onset cases of DM-2 (7.5%) over 11 years.

4. Adjusted odds ratios (**OR**) for DM-2 by lifestyle risk factors:

	OR for DM-2	% lower risk
BMI		
18.5-24.9	0.30	70
25 and above	1.00 (reference)	
Diet score		
Top 2 quintiles	0.85	15
Bottom 3	1.00	
Smoking		
Never	0.76	24
Current	1.00	
Moderate alcohol		

Yes	0.81	19
No	1.00	
Physical activity		
Yes	0.76	24
No	1.00	

5. A strong inverse dose-response relation was observed between number of lifestyle factors in the low-risk category and odds ratios for DM-2. Compared with adults with no lifestyle factors in the low-risk category, and excluding BMI, the ORs for men with 1,2,3 or 4 low-risk factors, were 0.79, 0.66, 0.56, and 0.45.

6. Association between specific combinations of factors in the low-risk category and adjusted ORs for new onset DM-2.

	OR	Lower risk (%)
Diet in the top 2 quintiles		
and regular physical activity	0.72	28
All other categories	1.00 (referent)	
Never smoking		
All others	0.68	32
All others	1.00	
Moderate alcohol		
All others	0.61	39
All others	1.00	
BMI 18.5-24.9		
All others	0.28	72
All others	1.00	

7. When family history of DM-2 was factored in, there was no increase in risk of DM-2.

DISCUSSION

1. In this large prospective cohort age 50-71, participants with low-risk lifestyle profiles at baseline that included: optimum BMI, engaging in regular physical activity, consuming a healthful diet, using alcohol in moderations, and not smoking, had, over 11 years, a dramatically lower risk of incident DM-2 than those without such profile.
2. Each additional factor was associated with a lower risk for DM-2.
3. Adiposity was the strongest risk factor for DM-2. However, even after adjusting for adiposity, regular physical activity, a healthy diet, not smoking, and moderate alcohol intake predicted a lower risk. This suggests that these factors affect the risk for DM-2 independently of the effects of adiposity.
4. A 19% lower risk for DM-2 was observed among men who consumed alcohol moderately

compared with those who were abstainers. Women had a 37% lower risk. Insulin resistance is important in the development of DM-2. Light-to-moderate alcohol consumption is associated with enhanced insulin sensitivity. It also has a moderate anti-inflammatory effect.

5. Another study reported that, after cessation of smoking, risk of DM-2 gradually decreased.
6. Overweight and obese adults may benefit by adopting the remaining low-risk lifestyle factors.
7. Many persons mistakenly believe that development of DM-2 is inevitable owing to their family history of DM-2. This study did not confirm this belief. Similar results were found among those with and without a family history.

CONCLUSION

A low risk profile composed of 5 lifestyle factors was strongly associated with a lower risk of new-onset DM-2 among older adults.

This has major implications for public health.

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1 This may not be a representative sample of the population.

Note: I abstracted only results for men. Results for women were broadly similar. But the combined influence of these factors in women had a slightly stronger association with low risk for DM-2