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FOR

PRIMARY CARE MEDICINE

ABSTRACTED MONTHLY FROM THE JOURNALS

A Free Public-service Publication

NOVEMBER 2011

JAMA, NEJM, BMJ, LANCET
ARCHIVES INTERNAL MEDICINE
ANNALS INTERNAL MEDICINE

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26th YEAR OF PUBLICATION

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 reviews 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.
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HIGHLIGHTS AND *EDITORIAL COMMENTS* NOVEMBER 2011

A Graded Inverse Association Between The Number Of Healthy Lifestyle Factors And Risk Of Stroke

11-1 LIFESTYLE FACTORS AND THE RISK OF ISCHEMIC AND HEMORRHAGIC STROKE

Healthy lifestyle factors (**HLF**) included: physical activity, smoking abstinence, modest alcohol consumption, body mass index (**BMI**), and diet.

This study assessed the individual and joint associations of multiple lifestyle factors with the risk of stroke.

Five independent cross sectional population surveys (n = 36 686) were performed between 1982 and 1997 across Finland. Participants were aged 25 to 74. None had a history of coronary heart disease or stroke.

Prospectively investigated the associating of different indicators of lifestyle and total, ischemic, and hemorrhagic stroke.

Followed the cohort until the end of 2007, a mean follow-up of 14 years.

Only 7% of the subjects observed all 5 HLFs. At baseline, they were much healthier that those with fewer HLFs—lower BMI, total cholesterol, and BP. None were smokers. They were more active, ate more vegetables, and used alcohol modestly.

During 14 years of follow-up, there were 1478 strokes—1167 ischemic; 311 hemorrhagic:

	Healthy lifestyle factors (men and women combined)				
	0-1	2	3	4	5
Participant no.	3976	9161	12093	8713	2743
Total stroke cases	326	480	449	195	28
%	9.2	5.2	3.7	2.2	1.0

Each of the HLFs was significantly associated with a reduced risk of ischemic stroke.

PA and vegetable consumption were inversely associated with stroke; smoking and BMI were directly associated. Only smoking was significantly associated with hemorrhagic stroke.

Alcohol showed a J–shaped association with ischemic stroke, with a higher risk at low-level and high-level consumption. Those with light-to-moderate consumption had the lowest risk.

The inverse associations between the numbers of HLFs and stroke persisted in those with hypertension, diabetes, and total cholesterol over 250.

In this large, prospective study, a combination of HLFs was associated with substantially

reduced risk of stroke. Those with all 5 HLFs had significantly decreased risk of total, ischemic, and hemorrhagic stroke. The stroke risk progressively decreased as the number of HLFs increased. This suggests that, in the population, most strokes could be avoided.

The inverse association between physical activity and stroke risk remained significant after controlling for hypertension, diabetes, and total cholesterol levels.

Conclusion: There was a graded inverse association between the number of HLFs and risk of total, ischemic and hemorrhagic st

(Read the full abstract for details and the citation . Ed.).

The benefit / harm-cost ratio of HLFs is huge. Harms and costs are nil. The risk of stroke over 14 years was reduced from 9% to 1%. If a drug produced these benefits, with no harm and low cost, it would become the biggest blockbuster in history.

I can imagine the drug company advertising their preparation reduces risk of stroke by 50%.

HLFs are also related to lower risk of diabetes(see Practical Pointers September 2011), congestive heart failure, myocardial infarction, and cardiac death.

A healthy diet includes: whole wheat, oils, and nuts. PA could be increased. Abstinence from alcohol continues to be a risk factor. I believe that additional studies will include fruit as an important healthy food.

Most studies assess only leisure-time PA. I believe adding work-time PA improves prognosis.

Primary care clinicians are (or should be) masters of preventive-care medicine. The majority of interventions they advise are preventive (eg, control of lipids, hypertensions, diabetes, obesity).

Primary care is primarily preventive care.

Preventive care is predominantly lifestyle care.

Necessitates An Ongoing Series Of Quit Attempts.

11-2 CHRONIC DISEASE MANAGEMENT FOR TOBACCO DEPENDENCE

Currently, models for tobacco cessation involve discrete episodes of care, usually combining behavioral and pharmacologic strategies delivered during 6 to 12 weeks.

The chronic nature of drug dependence (including nicotine) has been compared with other medical disorders such as diabetes and hypertension. In 2000, the US Public Health Service designated tobacco dependence a chronic disease. However, current tobacco treatments do not incorporate principles of chronic disuse management.

These investigators ask whether integration of smoking reduction as an intermediate goal has potential to keep smokers engaged in the quit process. Smoking reduction might decrease nicotine dependence, increase motivation to quit, and elicit additional attempts to quit.

This study also asks whether a longitudinal care approach—modeled on principles of chronic disease management—is more effective than discrete episodes of state-of-the-science treatment to promote smoking abstinence. The trial incorporated interim smoking reduction as an option for smokers who relapse, and emphasized daily cigarette reduction as a step toward the goal of abstinence.

This randomized, controlled trial (2005-2007) compared long-term tobacco cessation outcomes between: 1) longitudinal care (**LC**; n = 222) and usual care (**UC**; n = 221). All were considered addicted smokers. The LC group received tobacco cessation treatment (combined behavior and pharmacologic therapy) for 1 year. The UC group received standard, evidence-based treatment that lasted 8 weeks..

Run-in phase: Both groups received identical behavioral and pharmacologic treatment. Counseling was done by telephone. Five scheduled calls took place over 4 weeks. Call content included problem solving skills, social support, medical support, and relapse prevention. Both groups received free nicotine replacement (patch, gum, or lozenge).

Usual care: These participants received one more call at 8 weeks and were told the treatment would be completed. If they wanted further treatment they were advised to contact other resources.

Longitudinal care: If a participant relapsed, counselors urged making another quit attempt, explaining that smoking reduction was an alternative to cessation, and provided positive reinforcement for this choice as a step toward quitting. Counselors stressed a goal of at least a 50% reduction from baseline amount.

Primary outcome = 6 months of smoking abstinence measured 18 months from the initial quit date.

Abstinence rates were slightly higher in the UC group until 6 months. Abstinence then stabilized in the UC group and continued to increase in the LC group.

At 18 months, 6-month abstinence was 30% in the LC group and 23% in the UC group.

Rates of abstinence	UC %	LC %
21 days	50	43
3 months	35	30
6 months	28	25
12 months	23	26
18 months	23	30

The median percentage of days reporting no cigarette use was 57% in the LC group and 30% in the UC group. Among those who did not quit, there was more smoking reduction in the LC group at all

times. At 12 months, those in the LC group smoked about 11 fewer cigarettes per day vs about 7 fewer in the UC group.

No serious adverse effects from nicotine replacement were reported.

A smoking intervention based on chronic disease management principles—targeting the goals of quitting, but incorporating failure: setting interim goals; and continuing care –was more effective in achieving long-term abstinence than delivery of discrete episodes of care for cessation.

The chronic disease model may be more effective because it provides more intensive care and a long-term relationship and more social support.

Incorporating a reduction strategy permitted counselors to avoid framing relapse as a failure.

The LC model reinforces the notion that cessation may necessitate an ongoing series of quit attempts. It also allows counselors to adjust treatments in response to smoker's ongoing experience with quitting. This intervention strategy incorporates the probability of interim relapse.

Conclusion: A chronic disease model of care for treatment of tobacco dependence was more effective than discrete episodes of care. Clinical interventions should acknowledge the likelihood of relapse and incorporate this interim outcome into ongoing work toward the goal of complete abstinence.

(Read the full abstract for details and the citation . Ed.).

This is a complex, difficult-to-abstract article. It is a new approach to smoking cessation, which I believe has merit. I will be more convinced when a longer-term report of abstinence (5 years) is reported.

Considering the prevalence and magnitude of risk from smoking, application of a new approach is needed.

Primary care clinicians may not be able to duplicate the detailed counseling applied in the study but they can adopt a long-term approach that incorporates repeated cessation attempts and a plan to repeatedly reduce the number of cigarettes smoked with each quit attempt.

Primary care clinicians are able to provide care, support, and a long-term relationship required to achieve abstinence.

A never-give-up approach is needed. Note that participants in the LC group averaged about 8 attempts to quit.

11-3 THE CARDIOVASCULAR BIOMARKER CONUNDRUM

Defined broadly, a biomarker is a physiological variable that can be measured objectively and reliably, and connotes some biological characteristic about a patient. As such, biomarkers can be used

1) as a surrogate for a clinical endpoint; 2) to provide prognostic information and 3) as a tool to influence treatment strategies.

Biomarkers as Surrogates for Clinical Endpoints:

The use of biomarkers as a surrogate for hard endpoints—ie, important clinical outcomes such as morbidity and mortality—remain fraught with challenges, and must be used with caution.

"Surrogate endpoints (no matter how robust) can provide misleading information regarding the treatment endpoint." (Ie, the assumption that treating the biomarker will lessen risk of disease. Ed.)

We must set a lofty bar for biomarkers as surrogates for major clinical outcomes. Markers must track with a hard endpoint (without any medication intervention); must continue to track the endpoint (under the influence of an intervention); and must be correlated across several broadly different classes of intervention before any change in the biomarker might be reliably interpreted as implying any improvement in the clinical outcome.

Biomarkers for Prognosis:

In clinical practice, biomarkers are being used to convey prognostic information—to provide information beyond that available by using clinical variables. The Framingham Risk Score (**FRS**) is a good example. It is widely used, but has flaws.

Biomarkers to Tailor Therapy

A prediction test is used to delineate patients who would benefit from preventive therapy versus those who would not benefit.

Predictive biomarkers need to identify subsets of patients who might benefit when reasonable numbers are treated.

Biomarkers do hold promise in cardiovascular medicine. The promise has the greatest importance and immediacy when they are used as predictive tests

(Read the full abstract for details and the citation . Ed.).

Biomarkers are important in primary care medicine.

Biomarkers are determined by some type of screening or testing, which may be simple or complex; may be inexpensive or costly: may ultimately cause harm or be harmless.

Simple observation (obesity); simple history (menopausal symptoms)

Simple screening (BP determination; blood sample for lipids; Pap smear)

Imaging (mammography; CT of chest for nodules; CT of coronary arteries for calcium)

Invasive (colonoscopy)

Screening for a biomarker may cause harm and be costly. (Cost is an increasing concern.) CT is associated with significant radiation exposure. Colonoscopy has a risk of bleeding and perforation. CT of coronary arteries often reveals a non-calcified nodule in the lungs, which causes anxiety, bother, and requires expensive follow-up. Informing a patient about a biomarker may lead to "labeling", causing long-term anxiety.

Screening leads to preventive therapy, which may be categorized as secondary or primary:

Secondary prevention—preventive therapy for patients with established disease (eg, myocardial infarction or stroke—high-risk patients) is well established in clinical practice. History serves as the chief biomarker. However, many patients go on to develop a second episode despite therapy. The absolute reduction in risk from preventive therapy is less than the absolute reduction in risk from primary prevention. Many patients experience a recurrence despite preventive therapy.

Primary prevention—can apply to patients at low risk for the disease or at high risk. Not all patients considered for primary prevention are equally at risk. In primary prevention, the benefit/ harm-cost ratio (B / H-C ratio) varies, depending on whether it is applied to 1) a patient at low risk of an adverse outcome, or 2) at high risk. Patients with multiple biomarkers for a disease are at higher risk. The absolute risk reduction from primary preventive therapy is greater than the risk reduction achieved by secondary prevention therapy, especially if primary prevention is started early in life. A healthy lifestyle is the most beneficial and safest long-term primary prevention. However, if a drug is used for primary prevention, it may cause harm and be costly.

The perceived value of biomarkers and preventive therapy as judged by the B / H-C ratio can change over time. Some primary prevention therapies, which originally were thought to provide great benefit and were met with enthusiasm were eventually found to cause more harm and costs than first thought. The ratio becomes less than 1/1. Harms may not be recognized for years.

1) Low-dose aspirin to prevent a first myocardial infarction and stroke causes bleeding which outweighs any benefit in low-risk patients.

2) Prostate specific antigen screening, followed by prostatectomy causes more harms than benefits.

3) Estrogens to prevent cardiovascular events were ultimately found to increase their

incidence.

4) Vitamin D, multivitamins and minerals, and antioxidants are overused, increasing costs without benefit.

Some screening interventions have been used too frequently, causing false positives, increased costs and inconvenience:

1) Mammography: the B / H-C ratio before age 50 and after age 75 is low. Many false positives result in recall mammography and unnecessary biopsies.

2) Pap smear done too early in life and extended too far at old age result in increased costs and false positives.

3) EKGs are done too frequently as a "routine", increasing costs.

4) Intensive treatment of type-2 diabetes may increase mortality.

5) Osteoporosis screening too early and too often.

6) Other possible overuses: ankle/brachial index; carotid endarterectomy; CT scanning; MRI scanning. (If the equipment is available in the hospital or physician-owned, it will be used.)

How should primary care clinicians respond to these uncertainties?

1) Make a determination—is the patient at high risk or at low risk?

2) Use best judgment to evaluate the B / H-C ratio for individual patients.

3) Determine patients' understanding of the risks and benefits of preventive therapy and their personal preferences about screening. .

4). Continue advising healthy lifestyle for all. It has the highest B / H-C ratio of any intervention.

5) Advise patients to avoid multiple screenings offered in daily newspapers by itinerant providers.

6) Do not be the first to prescribe a new drug or screening test. Fashions in medicine change—usually slowly, but sometimes rapidly.

7) Be aware of "spin"" in reports of treatment trials supported by drug companies.

No wonder why primary care practice is so difficult to do well!

ED is an Independent Predictor of CVD.

11-4 THE EFFECT OF LIFESTYLE MODIFICATION AND CARDIOVASCULAR RISK FACTOR REDUCTION ON ERECTILE DYSFUNCTION

Erectile dysfunction (**ED**) is defined as a consistent inability to attain or maintain a penile erection of sufficient quality to permit satisfactory sexual intercourse. It is common. It has considerable impact on quality-of-life of middle-aged men.

ED shares modifiable risk factors with atherosclerosis and coronary artery disease (**CAD**): hypertension, diabetes, dyslipidemia, cigarette smoking, obesity, metabolic syndrome, and sedentary behavior. ED is highly prevalent in individuals with multiple cardiovascular disease (**CVD**) risk factors.

ED is an independent predictor of CVD**.**

Lifestyle modifications such as a healthy diet, exercise, and maintaining an active lifestyle has been shown to lessen ED.

This systematic review and meta-analysis of original randomized controlled trials, assessed the effect of lifestyle modifications of CVD risk factors on ED.

ED was measured by the International Index of Erectile Dysfunction (**IIEF**-5) using a score change as a continuous variable.

The study included 4 randomized, controlled trials (300 intervention subjects and 297 controls). Mean age of participants was 55. Study duration from 8 weeks to 24 months.

Interventions included exercise and other lifestyle changes, Mediterranean diet, and weight loss. Improving CVD risk factors in these trials was associated with statistically significant improvements in sexual function—a mean increase in the IIEF-5 score of 2.4 out of a total possible score of 25.

Therapy with oral phosphodiesterase inhibitors (eg, *Viagra*) is presently the most effective treatment of ED. Studies report improvements in IIEF-5 score of 10 points. Reduction of CVD risk factors may increase the scores beyond that resulting from the inhibitors alone.

There are several reasons to recognize ED as an early modifiable risk factor for CVD. Lead time between onset of ED and presentation of CVD may be several years. ED is an early manifestation of CVD and also an independent risk factor for CVD mortality and morbidity.

Men with ED represent a special population than may be more motivated to adopt a lifestyle to improve sexual function, and thus reduce risk of CVD.

Men recognize ED early, in contrast to risk factors for CVD, which are often recognized after irreversible vascular damage has been done. Increased awareness that ED is associated with CVD risk may provide an opportunity for earlier modification of CVD risk factors.

Recognition of E D in primary care may provide the opportunity to change to a healthier lifestyle.

This study strengthens the evidence that the maintenance of sexual function with lifestyle interventions also reduces CVD risk factors. Men with ED provide an opportunity to identify CVD risk and institute lifestyle interventions.

Archives Internal Medicine November 14, 2011; 171: 1797-1803 Original investigation, first author Bhanu P Gupta, Mayo Clinic , Rochester Minn

(*There were also 2 trials using a statin drug as the intervention. I omit this data. Ed***.)**

1 Google: International Index of Erectile Dysfunction (IIEF-5)

This is a weak study. The authors admit it is underpowered.

Importantly, ED may present an early opportunity to intervene with preventive measures for CVD, mainly lifestyle changes.

However, some men may be more concerned about loss of erectile function than risk of CVD.

Whole Grain, and Not the Fiber Content Alone, Has Beneficial Effects.

11-5 FIBER AND PREVENTION OF COLORECTAL CANCER

A systemic review and dose-response meta-analysis of prospective studies asks if high intake of dietary fiber or whole grains reduces the incidence of colorectal cancer. (**CRC**)

A 2007 report from the World Cancer Research Fund Report stated that dietary fiber probably protects against CRC. It is not clear whether specific types of fiber or whole grains are associated with risks of CRC.

This study suggests that, in addition to a high total dietary fiber, intakes of cereal fiber and whole grains may reduce the risks.

A literature search up to 2010 found 16 applicable studies of prospective cohorts. All investigated the association between intake of dietary fiber and whole grains with incidence of CRC.

The summary relative risk (**RR**) of CRC for each 10 g/d intake of dietary fiber:

Type of fiber	RR	
Total fiber	0.90	
Fruit	0.93	
Vegetable	0.98	
Legume	0.62	(very large confidence interval)
Cereal	0.90	
Whole grain	0.83	(3 servings daily)

(Only total and cereal fiber and whole grain were statistically significant.)

Because the observed associations were of weak to moderate size and no study reported results stratified by confounding factors, the possibility of residual confounding cannot be excluded.

An editorial[2] in this issue of BMJ comments:

The meta-analysis indicates that it is the whole grain, and not the fiber content alone that has beneficial effects.

A link between intake of dietary fiber and whole grains and a lower risk of colon cancer was first hypothesized in 1988. But randomized trials failed to support this association.

This is a classic situation within nutritional epidemiology: a food item is related to decreased incidence of a disease, and the biological effect is attributed to a single component. But when this component is tested in randomized trials the results are not as expected.

This ought to have taught researchers to study the dietary source, and not only one specific component.

A systematic review and meta-analysis of prospective observational studies reported in this issue of BMJ avoided this error. It clearly showed that a high intake of fiber from cereals and whole grains is significantly associated with a reduced risk of colon cancer. No preventive effect was seen with other sources of dietary fiber.

Fruits, legumes, vegetables and grains are main sources of dietary fiber. The first 3 have received major interest in cancer epidemiology. Fruits and vegetables have been considered especially important in preventing cancer, although more recent research has questioned this. Grains have received considerably less interest.

Whole grains, by definition, contain all fractions of the cereal product. But since the industrial revolution, people have favored white flour. In 2001, an analysis of whole grain found intake to be extremely low. A third of UK adults failed to consume any whole grain foods, and 90% consumed less than 3 servings a day. Intake was also low in the US.

When refining grain, most of the germ and bran—and therefore most of the bioactive compounds—are removed. Depending on the type of grain, about 80 % of the fiber and substantial amounts of essential minerals, vitamins and bioactive compounds are lost.

The meta-analysis adds to the current evidence of the many health effects of whole grains. Observational studies have shown that whole grains foods probably protect against obesity, type-2 diabetes, and cardiovascular disease.

From a public health point of view, whole grain foods are important. Evidence in their favor is rapidly accumulating. To increase intake of these foods in Western countries, the health benefits must be actively communicated and accessibility of whole grain products greatly improved, preferably with simple labeling system that helps consumers choose products with high whole grain content.

Types of fiber differ between different food groups. Although a high intake of whole grain can be recommended, research is still needed to explain the biological mechanisms responsible, including effects of different types of grains. There is some indication that whole grain rye may be more beneficial than other types of whole grains.

There are barriers to intake of whole grains. Some people might think that whole grains are less tasty. However, at least for children, limited availability of whole grains in the household, and not preference, has been shown to be the major obstacle to intake.

With time, people may even find that they prefer whole grains

BMJ November 26, 2011; 342: 1082 "Dietary fibre, whole grains, and risk of colorectal cancer" "Research article" first author Dagfinn Aune, Imperial College, London. BMJ2011;343:d6617

2 BMJ November 26, 2011; 343: 1075 Editorial by Anne Tjonneland, Institute of Cancer Epidemiology, Danish Cancer Society, Copenhagen

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I believe parents should regularly serve whole grain products to their young children, so the children may develop a liking for them.

FULL ABSTRACTS NOVEMBER 2011

A Graded Inverse Association Between The Number Of Healthy Lifestyle Factors And Risk Of Stroke

11-1 LIFESTYLE FACTORS ON THE RISK OF ISCHEMIC AND HEMORRHAGIC STROKE

Primary prevention (in patients without a history of stroke) is the most effective strategy in controlling stroke and its consequences. There is good evidence that a healthy lifestyle can reduce the risk of cardiovascular disease, and that a combination of several lifestyles can be more effective than any one factor in lowering risk

Healthy lifestyle factors (**HLF**) included: physical activity, smoking abstinence, modest alcohol consumption, body mass index (**BMI**), and diet.

This study assessed the individual and joint associations of multiple lifestyle factors with the risk of stroke**.**

STUDY

1. Five independent cross sectional population surveys (n = 36 686) were performed between 1982 and 1997 across Finland. Participants were aged 25 to 74. None had a history of coronary heart disease or stroke. All completed a self-administered questionnaire on medical and socio-economic factors, including the lifestyle factors.
2. Prospectively investigated the associating of different indicators of healthy lifestyles and total, ischemic, and hemorrhagic stroke.
3. These investigators previously had found that moderate and high occupational or leisure-time physical activity (**PA**) independently and significantly reduced stroke risk. These activities were merged into 3 categories: 1) Low—when participants reported light levels of both occupational and leisure PA; 2) Moderate—when participants reported a moderate or high level of either occupational or leisure-time PA; 3) High—when individuals reported a moderate or high level of both occupational and leisure-time PA.
4. Smoking was classified as never, ever, or current.
5. Alcohol consumption per week—none, 1 to 34 grams, 35 to 209 grams, and 210 or more in men, and 1 to 34, 35 to 139, and 140 or more in women.
6. Frequency of vegetables and fruits over the past week— <1, 1 to 2, 3 to 6, and 7 and over. However, fruit consumption was dropped from the analysis because no statistically significant association with stroke was found.
7. BMI was calculated.
8. All analyses were adjusted for age, education, family history, and for potential intermediate

factors such as diabetes and hypertension.

9. Followed the cohort until the end of 2007, a mean follow-up of 14 years.

RESULTS

	Number of Healthy Lifestyle Factors				
1. At baseline:	0-1	2	3	4	5
Participants No. (%)	3976 (11)	91619 (25)	12 093 (33)	8713 (23)	2743 (7)
BMI	28.3				22.5
Systolic BP	143				130
Total cholesterol (mg/dL)	235				204
Alcohol (g/week)	73				49
Moderate-high PA (%)	48				100
Vegetables 3 or more/week (%)	8				100
Smoking (%)	51				0

(At baseline, subjects who complied with all 5 HLFs were the healthiest.)

2. During 14 years of follow-up, there were 1478 strokes—1167 ischemic; 311 hemorrhagic:

	Healthy lifestyle factors (men and women combined)				
	0-1	2	3	4	5
Participant no.	3976	9161	12093	8713	2743
Total stroke cases	326	480	449	195	28
%	9.2	5.2	3.7	2.2	1.0
4. Hazards ratio					
Total stroke	1.00	0.66	0.57	0.51	0.33
Ischemic stroke	1.00	0.67	0.60	o.50	0.30
Hemorrhagic stroke	1.00	0.63	0.49	0.49	0.40

Each of the HLFs was significantly associated with a reduced risk of ischemic stroke.

5. PA and vegetable consumption were inversely associated with stroke; smoking and BMI were directly associated. Only smoking was significantly associated with hemorrhagic stroke.

6. Alcohol showed a J–shaped association with ischemic stroke, with a higher risk at low-level and high-level consumption. Those with light-to-moderate consumption had the lowest risk.

7. The inverse associations between the numbers of HLFs and stroke persisted in those with hypertension, diabetes, and total cholesterol over 250.

DISCUSSION

1. In this large, prospective study, a combination of HLFs was associated with substantially reduced risk of stroke. Those with all 5 HLFs had significantly decreased risk of total, ischemic, and hemorrhagic stroke.
2. The stroke risk progressively decreased as the number of HLFs increased. This suggests that, in the population, most strokes could be avoided.
3. Overweight and obesity have been found to increase risk of stroke in various observational studies. Obese women (BMI > 30) had a 1.5-fold higher risk of total stroke, and a 1.7-fold higher risk of ischemic stroke compared with those with BMI < 25. A meta-analysis of observational studies reported that moderately increased physical activity had a protective effect on all 3 types of stroke.
4. In the present study, a combination of occupational and leisure-time physical activity was associated with a reduced risk of stroke. Vegetable intake was also associated with reduced risk, but fruit intake was not.
5. The associations with alcohol have been J-shaped in most studies, with the lowest risk being in light drinkers.
6. The Women's Health Study showed that combinations of HLFs reduce risk of ischemic stroke, but not hemorrhagic stroke.
7. The present study showed a graded, inverse association between the number of HLFs and the risks of total, ischemic, and hemorrhagic stroke among both men and women.
8. In the present study, the inverse association between physical activity and stroke risk remained significant after controlling for hypertension, diabetes, and total cholesterol levels.

CONCLUSION

There was a graded inverse association between the number of HLFs and risk of total, ischemic and hemorrhagic stroke.

Archives Internal Medicine November 14, 2011; 171: 1811-18 Original investigation, first author Yurong Zhang,

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Necessitates An Ongoing Series Of Quit Attempts.

11-2 CHRONIC DISEASE MANAGEMENT FOR TOBACCO DEPENDENCE

Most smokers report they would like to quit. About 1/3 attempt to quit each year. Most smokers relapse within 3 months. Fewer than 10% are successful.

Currently, models for tobacco cessation involve discrete episodes of care, usually combining behavioral and pharmacologic strategies delivered during 6 to 12 weeks.

Long term abstinence (6 to 12 months), when the individual is no longer receiving medication constantly, is lower than abstinence at the end of treatment. Relapse continues.

Would prolonged treatment increase long-term abstinence?

The chronic nature of drug dependence (including nicotine) has been compared with other medical disorders such as diabetes and hypertension. In 2000, the US Public Health Service designated tobacco dependence a chronic disease. However, current tobacco treatments do not incorporate principles of chronic disuse management.

Smokers who relapse after a quit attempt are generally considered failures. This neglects the fact that some persons who resume smoking do so at a reduced level and maintain some smoking reduction long-term.

These investigators ask whether integration of smoking reduction as an intermediate goal has potential to keep smokers engaged in the quit process. Smoking reduction might decrease nicotine dependence, increase motivation to quit, and elicit additional attempts to quit.

This study also asks whether a longitudinal care approach—modeled on principles of chronic disease management—is more effective than discrete episodes of state-of-the-science treatment to promote smoking abstinence. The trial incorporated interim smoking reduction as an option for smokers who relapse, and emphasized daily cigarette reduction as a step toward the goal of abstinence.

STUDY

1. This randomized, controlled trial (2005-2007) compared long-term tobacco cessation outcomes between: 1) longitudinal care (**LC**; n = 222) and usual care (**UC**; n = 221). The LC group received tobacco cessation treatment (combined behavior and pharmacologic therapy) for 1 year. The UC group received standard, evidence-based treatment that lasted 8 weeks.
2. Participants were men and women smokers age 18-80 with an interest in making an attempt to quit.

3. Run-in phase:

Both groups received identical behavioral and pharmacologic treatment. Counseling was done by telephone. Five scheduled calls took place over 4 weeks. Call content included problem solving skills, social support, medical support, and relapse prevention.

Both groups received free nicotine replacement (patch, gum, or lozenge).

4. Participants were then randomized.

A. Usual care:

These participants received one more call at 8 weeks and were told the treatment would be completed. If they wanted further treatment they were advised to contact other resources.

B. Longitudinal care:

Determined whether the participant had 1) become abstinent, 2) had relapsed, but had reduced the number of daily cigarettes, or 3) continued the original amount of smoking.

For those who became abstinent, counselors used relapse prevention strategies: 1) identification of future high-risk situations and skills to handle them; 2) methods to maintain abstinence, such as lifestyle changes. 3) building self-efficacy and social support, and 4) issues of weight and exercise.

If a participant relapsed, counselors urged making another quit attempt, explaining that smoking reduction was an alternative to cessation, and provided positive reinforcement for this choice as a step toward quitting. Counselors stressed a goal of at least a 50% reduction from baseline amount. Strategies for delaying smoking, eliminating cigarettes in specific situations and scheduling reductions were discussed.

Counselors aimed to call every 2 weeks.

If the participant chose to make neither a quit attempt nor reduce smoking, they were asked again if they wanted to set a quit date or to reduce the number of cigarettes smoked.

Medication could be used for repeated quit attempts or to maintain smoking reduction. The nicotine replacement drug could be changed, and the dose increased.

Primary outcome = 6 months of smoking abstinence measured 18 months from the initial quit date.

RESULTS

1. Randomized 443 individuals: 222 to LC of which 203 were reached for the 18 month follow-up; and 221 to UC of which 203 were reached for the 18 month follow-up.
2. At baseline, mean age = 42; mean number of cigarettes smoked per day = 18; age of starting

regular smoking = 18; mean cigarette dependence score = 4612 (range 0 to 60). (Ie, addicted smokers)

3. Smoking cessation: Abstinence rates were slightly higher in the UC group until 6 months. Abstinence then stabilized in the UC group and continued to increase in the LC group At 18 months, 6-month abstinence was 30% in the LC group and 23% in the UC group.

Rates of abstinence	UC %	LC %
21 days	50	43
3 months	35	30
6 months	28	25
12 months	23	26
18 months	23	30

(My calculations from Figure 3. Ed.)

4. A high rate of smoking at baseline, and the number of cigarettes smoked in the past week predicted lower rates of abstinence.
5. The median % of days of no cigarette use was 57% in the LC group vs 39% in the UC group.
6. There were only 7 additional quitters in the UC group after 8 weeks.
7. Daily cigarette use was recorded, starting at the quit day until the last contact. The median percentage of days reporting no cigarette use was 57% in the LC group and 30% in the UC group. Among those who did not quit, there was more smoking reduction in the LC group at all times. At 12 months, those in the LC group smoked about 11 fewer cigarettes vs about 7 fewer in the UC group.
8. Participants in the LC group made significantly more quit attempts (mean 8.7 vs 6.6). The number of telephone calls and the time spent in counseling was greater in the LC group. The LC group received more nicotine replacements during the trial, and used more dual nicotine replacements (eg, patch + lozenges). Replacement was continued during the year. LC treatment was more costly in terms of counseling and nicotine replacements.
9. No serious adverse effects from nicotine replacement were reported.

DISCUSSION

1. A smoking intervention based on chronic disease management principles—targeting the goals of quitting, but incorporating failure: setting interim goals; and continuing care –was more effective in achieving long-term abstinence than delivery of discrete episodes of care for cessation.
2. After one year of active treatment, the quit rate in the LC group continued to rise, suggesting

that longer duration of treatment might be more effective.

3. The chronic disease model may be more effective because it provides more intensive care and a long-term relationship and more social support.
4. Incorporating a reduction strategy permitted counselors to provide positive reinforcement for outcomes other than cessation. And to avoid framing relapse as a failure.
5. The LC model reinforces the notion that cessation may necessitate an ongoing series of quit attempts. It also allows counselors to adjust treatments in response to smoker's ongoing experience with quitting. This intervention strategy incorporates the probability of interim relapse.

CONCLUSION

A chronic disease model of care for treatment of tobacco dependence was more effective than discrete episodes of care.

Clinical interventions should acknowledge the likelihood of relapse and incorporate this interim outcome into ongoing work toward the goal of complete abstinence.

Archives Internal Medicine November 28, 2011; 171: 1894-1900. Original investigation, first author Anne M Joseph, University of Minnesota, Minneapolis

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11-3 THE CARDIOVASCULAR BIOMARKER CONUNDRUM

Defined broadly, a biomarker is a physiological variable that can be measured objectively and reliably, and connotes some biological characteristic about a patient. As such, biomarkers can be used 1) as a surrogate for a clinical endpoint; 2) to provide prognostic information and 3) as a tool to influence treatment strategies.

Biomarkers as Surrogates for Clinical Endpoints:

The use of biomarkers as a surrogate for hard endpoints—ie, important clinical outcomes such as morbidity and mortality—remain fraught with challenges, and must be used with caution. Cardiovascular medicine has witnessed several notorious examples of well-studied biomarkers in which the predicted benefits ultimately differed from the clinical endpoint:

1) Premature ventricular contractions (**PVC**), particularly after a myocardial infarction, were considered a "world-wide public health problem" in the latter half of the 20th century. Their frequency was shown to correlate with risk of death. A new generation of anti-arrhythmic drugs was then used to

suppress PVCs. The large Cardiac Arrhythmic Suppression Trial assessed the safety and efficacy of a practice that then was commonplace. Recruitment for the trial was actually hindered by physicians' reluctance to allow their patients to be entered into a trial with a 50% chance of not receiving an "effective" drug (encainide, flecainide, and later moricizine). These drugs were later shown to correlate with increased mortality.

2) High-density lipoprotein cholesterol: Torcetraib, a cholesterol ester transferase inhibitor provided another cautionary tale when biomarkers substitute for clinical endpoints. The drug reliably increased HDL-cholesterol. Ultimately it was shown to increase cardiovascular mortality.

"Surrogate endpoints (no matter how robust) can provide misleading information regarding the treatment endpoint." (*Ie, the assumption that treating the biomarker will lessen risk of disease. Ed*.)

We must set a lofty bar for biomarkers as surrogates for major clinical outcomes. Markers must track with a hard endpoint (without any medication intervention); must continue to track the endpoint (under the influence of an intervention); and must be correlated across several broadly different classes of intervention before any change in the biomarker might be reliably interpreted as implying any improvement in the clinical outcome.

A novel biomarker may harbor a negative unexpected effect, and require years of validation and testing.

The use of biomarkers as surrogate endpoints remains a difficult and distant goal.

Biomarkers for Prognosis:

In clinical practice, biomarkers are being used to convey prognostic information—to provide information beyond that available by using clinical variables.

The Framingham Risk Score (**FRS**) is a good example. It is widely used. A variety of biomarkers is used to predict 10-year risk of coronary heart disease (age; BP; LDL or total-cholesterol levels; HDL cholesterol; smoking and diabetes.) Many articles have described enhanced ability of the score to predict outcome. But most studies had flaws in design that cast doubt on the ability of FRS to improve prediction. Newer prediction models beyond the FRS show that many persons would be reclassified.

Biomarkers to Tailor Therapy

A prediction test is used to delineate patients who would benefit from preventive therapy versus those who would not benefit.

The recent JUPITER trial attempted to validate a novel predictive biomarker for use of a statin drug in older patients with "normal" cholesterol and an elevated high sensitivity C-reactive protein.

(hs-C-RP) It randomized patients with hs-C-RP (> 2 mg/L) to the statin or no statin. Use of the drug lowered hs-C-RP levels and improved cardiovascular endpoints and total survival at 2 years. However, for hs-C-RP to have been fully confirmed as a biomarker, the trial also would have recruited patients with normal hs-C-RP levels (< 2 mg/L), randomized them to receive statin or placebo, and shown that these patients did or did not benefit from statin therapy, or benefited only marginally at unacceptable costs.

A meta-analysis of trials of statin drugs for primary prevention (excluding patients with established cardiovascular disease), but including those at high risk, generated controversy by demonstrating that more than 200 patients would need to be treated for 5 years to save one life at high cost and risk of adverse drug effects.

Predictive biomarkers need to identify subsets of patients who might benefit when reasonable numbers are treated.

Biomarkers, however, do hold promise in cardiovascular medicine. The promise has the greatest importance and immediacy when they are used as predictive tests. The use of biomarkers as surrogates for major clinical outcomes remain a distant goal. The flurry of biomarker research has created a maze of possible uses. “Use of biomarkers as predictive tests represents the greatest promise and the shortest and most effective path out of the maze.”

JAMA November 16, 2011; 306: 2151-52 “Commentary”, first author Vinay Prasad, Northwestern University Feinberg School of Medicine, Chicago, IL

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