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**ADDED SUGAR INCREASES RISK OF CARDIOVASCULAR DISEASE [3-1]**

**STRATEGIES TO EASE THE BURDEN OF FAMILY CAREGIVING [3-2]**

**EFFICACY AND SAFETY OF NEW ORAL ANTICOAGULANTS [3-3]**

**DELAYED ANTIBIOTIC PRESCRIPTIONS FOR RESPIRATORY INFECTIONS [3-4]**

**E-CIGARETTES ARE A “GATEWAY” TO TOBACCO CIGARETTE SMOKING [3-5]**

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I hope you will find *Practical Pointers* interesting and helpful.

Richard T. James Jr. M.D.

Editor/Publisher.

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*Aim for 10% of calories or less from added sugar*

**3-1 ADDED SUGAR INTAKE AND CARDIOVASCULAR DISEASE (CVD) MORTALITY AMONG US ADULTS: Original Research**

Consumption of added sugar among Americans, including all sugar added to processing or preparing foods, increased from an average of 235 calories (59 grams) in 1977-78 to 318 calories (79 grams) per day in 1994-96. This change was mainly due to increased consumption of sugar-sweetened beverages. Consumption of added sugars remained high through 2008, especially among children.

Recommendations for added sugar vary substantially:

- 1) Institute of Medicine: Less than 25% of total calories
- 2) World Health Association: Less than 10%
- 3) American Heart Assn: Less than 100 calories (25 g) daily for women and less than 150 (37 g) for men.

The 2010 Dietary Guidelines for Americans recommends limiting total intake of discretionary calories (added sugars and solid fats) from 5% to 15% of daily calories.

Individuals who consume higher amounts of added sugar, especially sugar-sweetened beverages, tend to gain weight, have high rates of obesity, type-2 diabetes, dyslipidemia, hypertension, and CVD.

This study examined the time trends of consumption of added sugars as percentage of total daily calories using a series of nationally representative samples, and their association with CVD mortality.

**STUDY**

1. The National Health and Nutrition Examination Survey (NHANES) comprises a series of cross-sectional multistage probability surveys of the civilian, non-institutionalized US population. Beginning in 1999 it became a continuous program with every 2 years representing a cycle. Each survey included a household interview, and a physical examination.
2. The present study includes 2 components: a trend analysis of added sugar consumption and a study of added sugar consumption and its association with CVD mortality.
3. This study used data from 3 NHANES studies from 1988 to 2010. Study population = 31 147.
4. For the association analysis between the added sugar and risk of CVD mortality, this study used data from NHANES 1998-1994 linked through 2006 with mortality attributed to CVD.
5. Estimation of usual percentage of calories from added sugar included all sugars used in processed or prepared foods (eg, sugar-sweetened beverages, grain-based desserts, fruit drinks, dairy desserts, candy, ready-to-eat cereals, and yeast bread, but not naturally occurring sugars as in fruit and fruit juices. A 24-hour dietary recall was used for the estimates.

## RESULTS

1. Among US adults, the adjusted mean percentage of daily calories from added sugar increased from 15% in 1988-1990 to 16.8% in 1999-2004, and decreased to 14.9% in 2005-2010.
2. Most adults (70%) consumed 10% or more of calories from added sugar, and 10% consumed more than 25% in 2005-2010.
3. During a median follow-up of 15 years, 831 CVD deaths were documented. Age, sex, and race/ethnicity adjusted hazard ratios (HR) of CVD mortality across quintiles of the percentage of daily calories consumed from added sugar were: 100 (reference); 1.09; 1.23; 1.49; and 2.43. After adjustment for socio-demographic, behavioral, and clinical characteristics, HRs were: 1.00 (reference); 1.07; 1.18; 1.38; and 2.03.
4. Adjusted HRs were 1.30 among those who consumed 10% to 24.9% of daily calories from added sugar, and 2.75 for those consuming 25% or more.
5. These findings were largely consistent across age groups, sex, race/ethnicity, education, physical activity, and body mass index.

## DISCUSSION

1. These results suggest that the usual percentage of calories from added sugar among US adults increased from the late 1980s and decreased during 2005-2010. Most adults consumed more than 10% of their total calories from added sugar and approximately 10% of adults consumed 25% or more of calories from added sugar in 2006-10. Compared with those who consumed about 8% of calories from added sugar, those who consumed approximately 17% to 21% (quartile 4) of calories from added sugar had a 38% higher risk of CVD mortality. The relative risk was more than double for those who consumed 21% or more.
2. Major sources of added sugar: sugar-sweetened beverages, grain-based desserts, fruit drinks, dairy desserts, and candy. One 360-mL can of regular soda contains about 35 g of sugar (140 calories) or 7% of total calories (based on a 2000 calorie diet).
3. There are no universally accepted guidelines for added sugar consumption. The present analysis suggests that those who consume 10% to 24% of calories from added sugar had a 30% higher risk of CVD mortality. For those who consumed 25% or more, the relative risk was nearly tripled (HR = 2.7). Regular consumption of sugar-sweetened beverages (7 or more servings per week) was associated with increased risk of CVD mortality.
4. In the present study, the positive association between added sugar intake and CVD mortality remained significant after adjusting for conventional CVD risk factors such as high BP and total cholesterol. In addition, the observed association was consistent across age groups, sex, race/ethnicity (except for non-Hispanic blacks), educational attainment, physical activity, and BMI.
5. The biological mechanisms underlying the association between added sugar intake and CHD risk are not completely understood. Although observational studies are important in improving our understanding

of nutrient-disease relationships, they should not be directly interpreted as evidence of causal relationships without considering other lines of evidence.

## CONCLUSION

Most US adults consume more added sugar than is recommended for a healthy diet.

A high percentage of calories from added sugar is associated with significantly increased risk of CVD mortality.

Regular consumption of sugar-sweetened beverages is also associated with CVD mortality.

These results support current recommendations to limit intake of calories from added sugar in US diets.

JAMA Internal Medicine, April 2014; 174: 516-24 Original investigation, first author, Quanhe Yang, Centers for Disease Control and Prevention. Atlanta GA

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*Is added sugar truly an independent risk factor, or is it related to risks from obesity, diabetes, and hypertension. If so, why? What is the mechanism?*

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## 3-2 STRATEGIES TO EASE THE BURDEN OF FAMILY CAREGIVING

An article in this issue of JAMA describes an older woman who attempted suicide to escape the overwhelming burdens of caring for her ill and debilitated husband. This starkly illustrates despair that caregivers can feel. It illustrates the failure of the US healthcare system to support them.

Half a century ago, when Medicare began, few people lived with disabling chronic illness and family supporters were readily available. Today, 65-year olds, and all who come after, are likely to experience several years of needing another person's help in the last phase of life. Many will find such help difficult to obtain. Few live near large, extended families, and few have younger family members who can afford to leave work to provide care.

Health care delivery services have not adapted to these needs.

Untrained and unpaid family caregivers must handle medical devices, medications, and treatments. They provide most of the hands-on care, often for years without a break, without pay, vacation, recognition, backup, or help.

Medical records typically do not have a place to identify family caregivers or to document an assessment of the ability to provide services their frailer elders need.

The end result is widespread and unnecessary suffering, isolation, fear, error and at times bankruptcy.

Without a vigorous response by clinicians and policy makers, this situation will worsen.

What should clinicians do to mitigate caregiver burdens?

- 1) Identify caregivers and ask them about their particular circumstances.
- 2) What resources do caregivers and the patient have?
- 3) What costs do they bear?
- 4) How will they manage?
- 5) What is their backup plan?
- 6) How are they coping?

Caregiving should demand coherent, practical, and comprehensive care plans. Clinicians should engage in developing them. Whenever new tasks and obligations arise, training and support for family caregivers are essential.

Every home situation has its breaking point that precludes continuing with the previously established arrangements. Clinicians must try to detect this risk through frequent monitoring.

Accomplishing the tasks imposed by medical care can require remarkable efforts by frail elderly persons and the caregiver. Reducing the complexity and time demands can help:

- 1) Simplify the medication schedule and diet instructions.
- 2) Provide a motorized lift and a video camera monitor.
- 3) Make home visits. Visiting the patient and caregiver in their environment provides opportunity to observe and ask about the caregivers burden capabilities, and needs.
- 4) Obtain consultations and diagnostic tests only when they are likely to contribute substantially to the care plan.
- 5) Community and neighborhoods need effective methods to identify people with progressively disabling chronic conditions and provide support.
- 6) Reviving neighborliness and supporting volunteer efforts are promising strategies for improvement.

Family caregivers often lose contact with friends, neighbors, relatives, and social groups. Frequently no one visits when the caregiver needs help, sympathy, and encouragement. Society should honor caregiving as a valued and expected part of life.

Clinicians can help by ensuring that their practice provides a mature and experienced staff person who knows about support available in the community, and helps families to make use of the appropriate resources. Physicians should be knowledgeable about city, county, and state resources.

Federal policy has been inattentive to family caregiving. Other developed countries assure that caregivers have health insurance, respite, continued contributions to retirement security, and income.

In many ways, caregiving defines the essentially shared nature of family life, from raising children to supporting older family members with progressive disability. Many caregivers speak to the privilege of selfless service to a loved one, even as they recount their burdens. Society will do well to nurture these human bonds.

Family caregiving is profoundly important as a tangible expression of the bonds of love and obligation. However, caregiving can also devastate families and individuals. Now that most people will eventually need caregivers, we need better policies and programs to support family caregivers.

JAMA March 12, 2014;311:1020-21 Editorial by Joanne Lynn, Altarum Institute. Washington DC

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*Busy primary care clinicians need experienced helpers to support caregivers. But they can visit the homes of their frail home-bound elderly patients, observe the conditions they live in, and the ability of their caregivers to cope with their burdens. Clinicians should at least acknowledge the caregiver's burdens and contribution and ask how they are coping.*

*Clinicians should also be aware of support available in the community by social services and other organizations.*

*The American Psychiatric Association has published a questionnaire to judge the severity of stress a caregiver may be undergoing. The Zarit Burden Interview consists of 22 questions about how the caregiver is feeling. Each answered by 0, 1, 2, 3, or 4 according to severity. Total scores range from 0 to 88. Scores between 61 and 88 indicate "severe burden".*

*To obtain a copy Google "The Zarit Burden Interview".*

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### **3-3 COMPARISON OF THE EFFICACY AND SAFETY OF NEW ORAL ANTICOAGULANTS (NOACs) WITH WARFARIN IN PATIENTS WITH ATRIAL FIBRILLATION (AF): Meta-analysis of randomized trials**

Vitamin K antagonists (eg, warfarin) are highly effective in preventing thromboembolism. Their use is limited by a narrow therapeutic index that necessitates frequent monitoring and dose adjustments resulting in substantial risk and inconvenience. This limitation has translated into poor patient adherence and underuse.

Several NOACs that dose-dependently inhibit thrombin or activated factor X (Xa) offer potential advantages—rapid onset and offset of action, absence of dietary vitamin K intake on their activity, and fewer drug interactions. Their predictable anticoagulant effects enable the administration of fixed doses without the need for routine monitoring.

They are at least as safe and effective as warfarin for prevention of stroke and systemic embolism (SE) in patients with AF. Dabigatran (thrombin antagonist), rivaroxaban and apixaban (Xa antagonists) have been approved. Endoxaban (a newer Xa antagonist) is awaiting approval.

This study presents an update of these NOACs as options to reduce risk of stroke in patients with AF.

## STUDY

1. Analyzed 4 RCTs (n = 71 673) comparing efficacy and safety of 4 NOACs with warfarin for prevention of stroke in patients with AF. Over 42 000 received a NOAC; over 29 000 received warfarin.
2. The NOACs included a thrombin inhibitor (dabigatran) and 3 Xa inhibitors (rivaroxaban, apixaban, and endoxaban)

## RESULTS

1. At baseline, the average age of participants was similar between trials. About 1/3 were over age 75. About 25% had paroxysmal AF; 50% had CHADS2 scores 3-6.
2. Median follow-up ranged from 1.8 years to 2.8 years.
3. In those with CHADS score from 3-6, 48% were in the NOAC group and 50% in the warfarin group.
4. Time in therapeutic range in patients on warfarin ranged from 58% to 68%.
5. All 4 RCTs showed greater benefit of NOAC vs warfarin for stroke and systemic embolic (SE) events:

NOAC	Warfarin
911/29312 (28%)	1107/29229 (37%)

6. Dose: (high doses were used)

Dabigatran	150 mg twice daily
Rivaroxaban	20 mg once daily
Apixaban	5 mg twice daily
Endoxaban	60 mg once daily



7. Efficacy:	NOAC (%)	Warfarin (%)	RR
Hemorrhagic stroke	0.40	0.90	0.49
Ischemic stroke	2.2	2.4	0.92 ns
Myocardial infarction	1.4	1.5	0.97 ns
All-cause mortality	6.9	7.6	0.90

The benefit of NOACs was largely due to a reduction in hemorrhagic stroke. There was also a reduction in all-cause mortality.

#### Safety

Intracranial hemorrhage	204/29287	425/29211	0.48
GI bleeding	751/28287	591/29211	1.25

Risk of GI bleeding was increased

8. The benefits of NOACs in reducing stroke was consistent across all subgroups of NOACs

9. A lower dose of NOACs resulted in efficacy similar to warfarin in reduction of stroke. An increase in ischemic stroke was balanced by a reduction in hemorrhagic stroke. Similar to high doses, low dose NOACs were associated with lower all-cause mortality, but significantly more myocardial infarctions than warfarin. Low dose was also associated with significant reductions in major bleeding. GI bleeding was similar between low dose and warfarin.

## DISCUSSION

1. Stroke and SE were significantly reduced in patients receiving NOACs, a benefit driven mainly by reduction in hemorrhagic stroke. Importantly, overall intracranial hemorrhage (including hemorrhagic stroke) was reduced by roughly half.

2. For prevention of ischemic stroke, NOACs had efficacy similar to warfarin, which itself is very effective in reducing ischemic stroke by 2/3 compared with placebo.

3. In general, NOACs have a favorable safety profile compared with warfarin. They are associated with significant reduction in all-cause mortality. However, they are associated with increase in GI bleeding.

4. Low dose NOACs show overall reductions in stroke or SE similar to warfarin. (Fewer hemorrhagic strokes, but more ischemic strokes.) They have a more favorable bleeding profile. They preserve the mortality benefit of high dose. Low-dose may be an appealing option for frail patients or for those with high-risk of bleeding with full anticoagulation.

5. This meta-analysis supports the premise that, compared with warfarin, the new oral anticoagulants, as a class, reduce all-cause mortality by about 10%.

6. Both the risk of stroke and bleeding increase with older age (>75), in patients with previous stroke, and those with renal dysfunction.

## SUMMARY

NOACs have a favorable risk-benefit ratio compared to warfarin, with significant reductions in hemorrhagic stroke, intracranial hemorrhage, and mortality, and with a similar major bleeding as for warfarin. GI bleeding is increased.

The relative safety and efficacy of the NOACs was consistent across a wide range of patients.

Lancet March 19, 2014;383:955-62 Original investigation, first author Christian T Ruff, Harvard Medical School, Boston Mass.

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*I am sorry to see the demise of the venerable warfarin.*

*The American Heart Association recommends NOACs for patients with AF.*

*They are certainly simpler and easier to administer than warfarin. But they are expensive.*

*I cannot think why GI bleeding is increased while hemorrhagic stroke is decreased.*

*I believe studies comparing advantages and disadvantages of individual NOACs will soon appear. Is there a "best"?*

*CHADS2 score: (a 6-point scale assesses risk of stroke in patients with AF)*

	<i>Points</i>
<i>C Congestive heart failure</i>	<i>1</i>
<i>H Hypertension or treatment for it</i>	<i>1</i>
<i>A Age 75 and older</i>	<i>1</i>
<i>D Diabetes</i>	<i>1</i>
<i>S Prior stroke or TIA</i>	<i>2</i>

*Patients with a score of 0 are at low risk for embolism. They may be treated with aspirin.*

*Those with a score of 1 are at moderate risk. They may be treated with aspirin or anticoagulation. Those with scores of 2 or more are at high risk. Anticoagulation is advised..*

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### **3-4 DELAYED ANTIBIOTIC PRESCRIBING (DABP) STRATEGIES FOR RESPIRATORY TRACT INFECTIONS IN PRIMARY CARE: Randomized controlled trial (RCT)**

This RCT asks—How effective are different strategies of DABPs in symptom control of acute respiratory infections? Systematic reviews of DABPs suggest worse symptom control than for immediate antibiotics.

This study demonstrates good symptom control and similar outcomes for different DABP methods.

#### **STUDY**

1. Of 889 patients over age 3 with an acute respiratory infection, 333 were prescribed immediate antibiotics. The remainder were randomized to different approaches of DABPs:

- 1) Immediate prescription
- 2) No prescription
- 3) Recontact for a prescription (Recontact)
- 4) Post-dated prescription (Post-date)
- 5) Return for collection of the prescription (Collection)
- 6) Giving the prescription to be used at the patient's discretion. (Patient led)

2. Main outcome: Symptom severity on day 2-4, and antibiotic use. Follow-up 1 month.

#### **RESULTS**

1. On a scale of 1 to 6, symptom severity at day 2 to 4 showed minimal differences between groups.
2. Median duration of symptom: no prescription—3 days; all delayed groups—4 days.
3. There were modest and non-significant differences in antibiotic use between groups.
4. Significantly more patients for whom antibiotics were prescribed for immediate use took them (97%), but with no benefit for symptom severity score or duration of illness (4 days). However, most patients believed the antibiotic helped.
5. Harms: complications occurred in 3 of 122 patients in the no prescription group, but this difference was not statistically significant. However, the trial was not powered for complications.

6. Effectiveness of antibiotic strategies in randomized groups:

Mean severity of symptoms days 2-4 on a scale of 0 to 6.

As above	1)	2)	3)	4)	5)	6)
Crude mean	1.76	1.62	1.60	1.82	1.68	1.75
Median duration						
moderate symptoms (days)	4	3	4	4	4	4
Antibiotic use (%)	97	26	37	37	33	39

7. Use of antibiotics was reduced about 60% in the DABP groups.

## CONCLUSION

Symptom control did not differ by strategy.

Either no prescription or delayed prescription resulted in fewer than 40% of those using an antibiotic.

This represents a decrease of over 60% in use of antibiotics.

BMJ March 15, 2014;348:14 Original investigation, first author Paul Little, University of Southampton, UK

BMJ2014;348:G11606

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*“Delayed” prescriptions (“if” prescriptions) are not new. Previous studies have reported the same reduction in antibiotic use. I believe the most common procedure in the US is for the physician to give a prescription for the antibiotic, admonishing the patient not to fill it for a day or two while observing the course of the infection. If symptoms do not improve or get worse, the prescription should be filled; if symptoms improve or stabilize, the prescription is not filled, and no antibiotic is taken. If the patient expresses a strong personal preference for an antibiotic, I would give it to him and request that he not fill it for a day or two.*

*Clinician judgment, as always, is essential. Giving or withholding an antibiotic prescription on the first visit depends on the physician’s clinical judgment. If the prescription is delayed, the physician’s office should follow-up by phone call in a day or two.*

*This approach works. Use of antibiotics will decrease if this strategy is followed. Development of antibiotic resistance may be delayed.*

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### **3-5 E-CIGARETTES (E-C) ARE “GATEWAY DEVICES” FOR SMOKING AMONG YOUNG PEOPLE**

A recent study from the US concludes that adolescents who use E-C are more likely to smoke conventional tobacco cigarettes (TC) and less likely to quit smoking.

“Nicotine delivery devices are unlikely to discourage conventional cigarette smoking among youths.”

Researchers from the University of California, San Francisco, looked at tobacco use among more than 40 000 pupils from middle and high schools across the USA. All completed questionnaires as part of a National Tobacco Survey.

The data, published in JAMA Pediatrics, showed that the number of adolescents who tried E-C more than doubled from 3.1% to 6.5% between 2011 and 2012.

Among adolescents called “experimenters”, ever having used an E-C was associated with being an established and current T-C smoker, as well as a current E-C smoker. Use of E-C was also associated with heavy smoking among those young people who also smoked conventional T-C, and reduced the chances of abstaining from conventional T-Cs for 30 days or more.

The researchers said these results “suggest that E-C use is aggravating, rather than ameliorating the tobacco epidemic among youth”. “Despite claims that E-C are helping people to quit smoking, E-C were associated with more, not less, T-C smoking among adolescents. E-cigarettes are likely to be gateway devices for nicotine addiction.”

The study did not allow researchers to identify whether adolescents started to use conventional T-C or E-C first. But about 20% of middle school students and about 70% of high school students who had ever used E-C had never used T-C, meaning that some are introduced to addictive nicotine through E-C.

Marketing of E-C is not only encouraging youth to smoke E-C, but is also promoting regular T-C smoking.

Adolescents who use E-C are less likely to stop using conventional cigarettes.

BMJ March 15, 2014;348:2 “News” by Zosia Kmietowicz, BMJ Staff.

BMJ2014;348:g2034

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*What a disappointment. I had hoped to learn that E-C would lead to less T-C use. And act as a gateway to quitting. Apparently not so.*

