

**PRACTICAL POINTERS**  
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***Begins At An Early Age. Progresses. Start Prevention Early***

**12-1 PREVALENCE OF, AND RISK FACTORS FOR, AUTOPSY-DETERMINED  
ATHEROSCLEROSIS AMONG US SERVICE MEMBERS 2001-2011**

Age-related atherosclerotic heart disease (AHD) mortality has declined by 72% since the peak in 1968, attributed equally to reduction in risk factors and improvements in therapies.

An early breakthrough in understanding the natural history of AHD was achieved in 1963, when the Armed Forces Institute of Pathology reported a 77% prevalence of coronary atherosclerosis (CAS) among US soldiers killed in the Korean war. By demonstrating anatomically that atherosclerosis affects a large proportion of young individuals who have no clinical evidence of heart disease, the study revolutionized the understanding of the onset and progression of AHD. Atherosclerosis begins at an early age.

Since then, health policies for children and young adults in the general population have been implemented to reduce risk of CAS associated with factors such as hypertension, diabetes, cholesterol, and smoking.

**STUDY**

1. This cross-sectional study determined the prevalence of atherosclerosis among US service members who died in Iraq and Afghanistan in support of combat operations or of unintentional injuries.
2. Demographic data included age, sex, race/ethnicity, highest education achieved, service branch and military rank.
3. Medical data included body mass index at military entrance, and major CAS risk factors—hypertension, dyslipidemia, obesity, diabetes, impaired fasting glucose, and smoking.
4. All military deaths associated with combat or with unintentional injuries require an intensive autopsy including all major coronary arteries. The pathologist documented the location and degree of all atherosclerotic lesions based on gross examination. Atherosclerotic lesions were classified as minimal (fatty streaks only) moderate (10% to 40% luminal narrowing in 1 or more vessels) and severe (50% or more narrowing of 1 or more vessels).

**RESULTS**

1. Included 3832 service members age 18 to 59, mean age 25, 98% white.

2. Prevalence of coronary and/or aortic atherosclerosis by demographic characteristics:

	No. with atherosclerosis/ Total No.	Atherosclerosis Prevalence %	Prevalence Ratio
Total	464/3832	12.1	1.00
Age			
<25	135/2047	6.6	1.66
25-29	103/931	11.1	1.68
30-39	154/697	22.1	3.35
40 & above	72/157	45.9	6.95S

Overall prevalence of coronary or aortic AS was 12.1%.

Age consistently produced the strongest association with CAS. Those with CAS were approximately 5 years older than those without. Those age 40 and older had about 7 times the prevalence compared with those age 24 and younger. (46% vs 6.6%; RR = 7)

3. Prevalence of any CAS was 8.5%: severe in 2.3%; moderate 4.7%; minimal in 1.5%.

5. Prevalence of any aortic AS was 5.7%

6. Prevalence of coronary and/or aortic atherosclerosis according to risk factors

Risk	No. with atherosclerosis/ Total No.	Atherosclerosis Prevalence %	Prevalence ratio
None	389/3506	11.1	1.00
Smoking	18/128	14.1	1.27
Obesity	37/166	22.3	1.47
Dyslipidemia	14/28	50.0	2.09
Hypertension	17/39	43.6	3.93

Lower education level and higher entrance BMI were significantly associated with CAS, after adjusting for age.

Those with BMI 25 to 29 (overweight) and 30 and above (obese) had a significantly higher prevalence of CAS (overweight 12.7% vs 7.6%; obese 15.8% vs 7.6%).

Age adjusted prevalence compared with those with no major CAS risk factors:

Dyslipidemia 50% vs 11%

Hypertension 44% vs 11%

Obesity 22% vs 11%

## DISCUSSION

1. The prevalence of coronary atherosclerosis among US service members was 8.5%.  
Older age, lower education level, higher BMI, hypertension and prior diagnosis of dyslipidemia were associated with higher prevalence of CAS.
2. This is a decline from 77% in the Korean war and 45% in the Vietnam war, although there were methodological differences between studies, and also some demographic and socio-economic differences. Comparisons should be made with caution.
3. Autopsies conducted for aviation mishaps over the past 5 decades generally demonstrate a decline in severe CAS. The prevalence of CAS risk factors in the general US population, with the exception of obesity and diabetes, has been trending down. A recent study of more than 280 000 Air Force members found lower prevalence of hypertension, dyslipidemia, and diabetes compared with the US general population.
4. Smoking rates have declined in the military. In 1980, 51% smoked; in 1998, 30%.  
The Department of Defense tolerated or even promoted tobacco use in earlier times. More recent policy initiatives aim to reduce smoking. Despite policy initiatives and improvements, smoking rates (30%) exceed civilian rates among similar age groups.
6. These findings suggest that the prevalence of CAS has declined among US service members. The prevalence in the general US population has declined over a similar period.
7. Targets for further improvement remain. Health care systems should continue to help patients reduce CVD risk beginning in childhood and continuing throughout adult life.

JAMA December 26, 2012; 308: 2577-83. First author Bryant J Webber, Uniformed Services University of Health Sciences, Bethesda MD.

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*Deaths in the Armed Forces due to combat during this period totaled 6191. My stomach turned when learning this.*

*I abstracted this article chiefly to again emphasize that CAS begins at an early age and progresses. It is preventable.*

*About 1 in 50 of the young cohort had severe CAS. Prevalence increased dramatically between ages 20 and 40. We can do better.*

*Smoking has indeed decreased, although far from being eliminated. During WW II, the Post Exchanges sold cigarettes for 50 cents a carton. Rations contained packets of free cigarettes. It was not until the 1950s that the true harms of smoking became clear.*

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### ***Modest Benefit From Fish. No Benefit From Supplements***

## **12-2 ASSOCIATION BETWEEN FISH CONSUMPTION, LONG CHAIN OMEGA-3 FATTY ACIDS, AND RISK OF CARDIOVASCULAR DISEASE: Systematic Review and Meta-analysis**

Fish consumption is considered one of the key components of a cardio-protective diet. Current guidelines encourage consumption of a variety of fish, preferably oily fish, at least twice a week.

Fish oils are the most common dietary sources of long-chain omega-3 fatty acids (O-3). Guidelines have recommended these nutrients in people with existing coronary heart disease—secondary prevention).

Whether, or to what extent, recommendations for consumption of fish and O-3 may apply to cerebrovascular disease (CVD) is not clear. Observational evidence is inconsistent. The results for CVD prevention are confusing. Recent large scale primary and secondary prevention trials have failed to show efficacy of supplementation with O-3 in reducing CVD.

This systematic review and meta-analysis of available studies quantified the association of fish consumption with total and cause-specific CVD; examined associations of dietary and circulating levels of O-3 with CVD in observational studies; and evaluated the potential effects of supplementation on cerebrovascular events in randomized, controlled trials.

### **STUDY**

1. Selected prospective cohort studies and randomized controlled trials reporting associations of dietary fish consumption and dietary O-3 consumption, or O-3 supplements, with CVD (any fatal or non-fatal ischemic stroke, hemorrhagic stroke, or transient ischemic attack). Both primary and secondary prevention studies were eligible.

### **RESULTS**

1. Overall, 38 unique studies met inclusion criteria and were included in the meta-analysis. In aggregate, the studies comprised 794 000 unique participants and 34 817 incident CVD outcomes from 15 countries.
2. Fish consumption and cerebrovascular risk:

Information was available in 21 prospective cohort studies (657 048 participants; 25 320 incident cerebrovascular events). All studies were based on general populations. There was no evidence of heterogeneity across studies.

The relative risk of CVD for fish intake of 2 to 4 servings per week vs 1 or fewer serving, was 0.94. And for 5 or more servings vs 1 or fewer servings a week was 0.88

In a dose-response meta-analysis, an increase of 2 servings per week of any fish was associated with a 4% reduced risk.

For all 21 studies, the relative risk when comparing participants in the highest with the lowest category of fish intake was 0.88.

In a subset of studies (62 799 participants) the relative risk for white fish was 1.03 and for fatty fish was 0.84.

Dose response: For each 2 servings of fish weekly, the relative risk of CVD was 0.96

Category of fish intake	No. of participant	No. of events	Relative risk
2-4 servings / wk	650 210	24 611	0.94
5 or more	394 958	16 890	0.88

### 3. Comparison with evidence from dietary O-3 studies:

Fourteen prospective studies reported on O-3 (305 119 participants; and 5374 cerebrovascular accidents over 4 to 30 years). Ten studies reported on dietary intake; 4 were based on circulating O-3 levels. All cohorts included healthy populations at baseline.

Relative risk for CVD for O-3 measured by circulating biomarkers was 1.04; and by self-reported dietary exposures was 0.90.

The corresponding relative risk in the top compared with the bottom third of baseline fish consumption was 0.91

	No of participants	No. of events	Relative risk
<b>O-3</b>			
Circulating O-3	4096	1177	1.04
Dietary O-3	301 023	4197	0.90
<b>Fish consumption</b>			
All CVD events	366 787	11 349	0.97
Ischemic stroke	284 178	5002	0.93
Hemorrhagic stroke	284 178	1783	0.81

#### 4. Effects of O-3 supplements on cerebrovascular risk

Twelve randomized trials (N = 62 040). Ten trials included participants with previous cardiovascular disease. (Secondary prevention) Two concerned populations without any preexisting cardiovascular disease.. (Primary prevention)

Participants in the intervention arm on average consumed 1.8 g of O-3. daily usually as a capsule.

After an average of 3 years, those with prior cardiovascular disease, a total of 800 cerebrovascular events occurred in the intervention group vs 763 in the controls. (Pooled relative risk = 1.03.)

The corresponding pooled relative risk for primary prevention (2 trials) was 0.98/ and for secondary prevention trials (10 studies) was 1.17.

Effects of O -3 supplements on CVD risk

	No. of participants /		Relative risk
	No. of events		
	Intervention	Control	
CVD	31 088/800	30 952/763	1.03

#### DISCUSSION

1. Higher fish consumption was moderately, but significantly, associated with reduced risk of incident cerebrovasccular disease. The overall relative risk of CVD when comparing the highest with the lowest category of fish intake was 0.87.
2. By contrast, dietary O-3, circulating biomarkers of O-3, and O-3 supplements were not significantly associated with risk of CVD.
3. These findings suggest that single nutrients may have limited effect on chronic disease outside their original food sources.
4. The associations with O-3 were consistent across people with and without pre-existing cardiovascular disease—indicating a potential lack of benefit for either primary or secondary prevention.
5. There may be several alternative explanations for these results.

It is possible that the potential benefit of fish could, in addition to O-3, be attributed to a wide variety of nutrients that are abundant in fish, (eg, vitamin D and B complex, essential amino acids, and trace elements).



The positive impact of fish could be explained by a concomitant reduction in intake of foods detrimental to cerebrovascular health, such as red meat. A recent analysis based on 2 large cohorts reported a 17% reduction in cerebrovascular risk when red meat intake was replaced with fish.

Higher fish consumption may simply be an indicator of a healthier dietary pattern or higher socioeconomic status and better medical services.

The method of cooking may be relevant. (eg, cooking white fish in oil vs battered and deep-fried).

Food composition tables are often incomplete and the actual O-3 content is not known, leading to underestimation of the true intake of O-3.

There is a substantial difference in quantity of O-3 between marine species.

In this analysis, circulating biomarkers of O-3 were not associated with CVD. Biomarkers reflect only exposure over several weeks, compared with the prolonged assessment that is more relevant to prediction of risk.

Competing risks such as coronary heart disease may have altered the possibility of CVD outcomes and impeded many subsequent events being considered.

Consumption of fish and O-3 has been also associated with reduced risk of coronary heart disease and sudden cardiac death.

6. This study reinforces the modest benefit of fish for CVD. The findings are in line with current dietary guidelines, which encourage fish consumption for all. And intake of fish oil, preferably from oily fish.
7. Nutritional guidelines should be primarily “food based”.
8. However, there are scientific gaps in the experimental evidence.

## CONCLUSION

Available observational data demonstrate moderate, inverse association of fish and O-3 consumption with risk of CVD.

There was no evidence of a similar inverse association from O-3 measured as circulating biomarkers in observational studies or supplements in primary and secondary prevention.

The benefits of fish might be mediated through a complex interplay among a wide range of nutrients commonly found in fish.

BMJ 2012;345:e6698 14 First author Rajiv Chowdhury, University of Cambridge, UK A brief abstract appeared in BMJ November 3, 2012;345

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*It makes more sense to me to consider fish rather than O-3 supplements to reduce risk. It is likely that components of fish (other than O-3) are protective. Eating fish several times a week will displace consumption of harmful red meat.*

*In comparative studies, it is more satisfactory to consider a distinct entity such as O-3 rather than a nebulous entity such as “fish”.*

*I believe the association also applies to coronary heart disease.*

*Save money, buy fish instead of supplements.*

=====

***Avoids Need For Fasting. Lower Biological Variability. Good Predictor Of Future Complications Of Diabetes. Can Be Used To Diagnose Diabetes In Most People. Many Exceptions***

### **12-3 USE OF HbA1c IN THE DIAGNOSIS OF DIABETES**

Before 2010, blood glucose levels were used to diagnose diabetes. Improved standardization of HbA1c and wider availability of the assay led to recommendations in 2011 by the WHO that HbA1c could be used for diagnosis. This recommendation was included within a recent UK public health guideline for identification of people at high risk of diabetes. In addition, a UK expert advisory group—after an extended period of consultation—stated how the HbA1c recommendations should be implemented.

The group recommended that a HbA1c cut-point of 48 mmol/mol (6.5%) or more should be used for diagnosis.

Unless the diagnosis is clear, a second confirmatory measurement is needed as soon as possible. If this is less than 48, the diagnosis of diabetes should not be made.

Patients with HbA1c of 42-47 should be considered at high risk for diabetes and provided with intensive lifestyle advice and retested annually.

Those with levels less than 42 may still be at high risk and should be treated according to clinical indications, with retesting at least every 3 years.

The group also recommended that glucose testing should not be carried out alongside, or after, HbA1c measurement for confirmation of the diagnosis unless the patient has a condition in which HbA1c cannot be measured accurately.

A major benefit of HbA1c is that it avoids the need for fasting. The biological variability of HbA1c, which reflects glucose exposure over the lifetime of the erythrocyte (120 days) is lower than that of glucose. HbA1c is also more stable than glucose when being transported to the laboratory.

HbA1c is a good predictor of future complications of diabetes, such as cardiovascular disease.

Assays for HbA1c vary. Achieving an acceptable level of precision requires analyses to be carried out in an accredited laboratory. Analysis is also more expensive.

A major concern is that, when recommending HbA1c as a diagnostic test, it may be used inappropriately.

The test should not be used to diagnose type 1 diabetes, in persons who are acutely ill, in children and young adults, in pregnant women, and in those who may have gestational diabetes. In these conditions, glucose values can change quickly, and HbA1c values may not accurately reflect glycemic exposure.

In acutely ill patients, glucose measurement should still be guided by finger stick capillary glucose.

HbA1c values are also affected by hemoglobin variants and hemolytic anemia and other conditions which affect erythrocyte survival. Severe iron deficiency should be treated before measuring HbA1c.

Most assays are based on immunochemistry of high performance liquid chromatography, and their use in specific circumstances needs to be guided by local laboratories.

Nevertheless, HbA1c can be used to diagnose diabetes in most people.

It is uncertain how much of the new diagnostic strategy will increase or decrease the prevalence of diabetes compared with the oral glucose tolerance test.

Undiagnosed diabetes is a serious public health problem.

The WHO recommendations, now endorsed by the expert advisory group aims to improve the detection of diabetes by making the process of testing easier.

BMJ November 10. 2012; 345: 10 Editorial by Andrew Farmer, University of Oxford, UK

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*Our chemistry friends have been able to determine HbA1c quantitatively. (In moles)*

*The article lists other situations in which HbA1c cannot be reliably used for diagnosis.*

*Primary care clinicians must be assured that the laboratory they use is reliable and consistent. And be aware of the restrictions and exceptions.*

*I believe many clinicians will still rely on blood glucose determination, which they are accustomed to and which are part of a routine biochemical profile, for diagnosis. Blood glucose is certainly more convenient, and available immediately at the point of care.*

=====

*Patients Already Taking Warfarin And Have Good Inr Control Have Little To Gain By Switching*

## **12-4 COMPARATIVE EFFECTIVENESS OF WARFARIN AND NEW ORAL ANTICOAGULANTS FOR THE MANAGEMENT OF ATRIAL FIBRILLATION AND VENOUS THROMBOEMBOLISM**

For decades, warfarin has resulted in important risk reduction of thrombotic events related to atrial fibrillation (AF), mechanical heart valves, and venous thromboembolism (VTE). Although bleeding remains a problem, protocols are available for reversal of over-anticoagulation by using vitamin K and blood products.

Warfarin (W) has a narrow therapeutic window, and wide variability in anti-coagulant effect. It requires regular monitoring. In practice, 30% to 50% of the time the International Normalized Ratios (INR) fall outside the therapeutic range.

Recently, new oral anticoagulants (NOACs) have emerged: 1) inhibitors of activated factor X (FXI), and 2) direct thrombin inhibitors (DTI). They have a more direct anticoagulant effect and eliminate the need for routine monitoring. But they lack specific antidotes to reverse bleeding. This is more worrisome when drug clearance may be prolonged as in the elderly and patients with renal impairment.

The FXI, rivaroxaban, is approved in the US for VTE prophylaxis during orthopedic surgery, and for stroke prophylaxis in patients with AF. The DTI, dabigatran, is approved in the US for stroke prevention in patients with AF.

They are expensive.

The Department of Veterans Affairs commissioned this systematic review to evaluate the comparative effectiveness of NOACs and W.

### **STUDY**

1. Developed and followed a standard protocol for all steps of this review.

2. Key questions:

For patients with chronic non-valvular AF, what is the comparative effectiveness of NOACs and W on stroke incidence and mortality?

For patients with VTE, are there differential effects of NOACs vs W on recurrent VTE, and mortality.

What are the nature and frequency of adverse effects of NOACs vs warfarin?

## RESULTS

### 1. Extensive literature search found 6 good-quality randomized studies involving

61 424 patients. Three studies evaluated NOACs for chronic AF; 3 evaluated treatment of VTE.

### 2. All studies compared NOACs vs adjusted-dose warfarin.

### 3. AF studies:

Three studies (n = 50 579; mean age > 70 ) compared apixaban, dabigatran, or rivaroxaban vs W for stroke prevention. Two studies modified the drug dosage for patients with impaired renal function and for older age.

In the control (W) group, the percentage of time in the INR target range was a median of 64%.

NOACs (compared with W) were associated with reduced:

All-cause mortality (RR = 0.88)

Ischemic stroke (RR = 0.89\*)

Hemorrhagic stroke (RR = 0.48)

(\* Not statistically significant.)

Other outcomes did not differ significantly.

Estimated absolute risk difference = 8 fewer deaths and 4 fewer hemorrhagic stroke for every 1000 patients treated with NOACs.

Subgroup analysis of 1 study suggested that, compared with those receiving W with good control, dabigatran may increase some bleeding complications, particularly in patients over age 75.

### 4. VTE studies:

Three studies (n = 10 846) evaluated dabigatran (1) or rivaroxaban (2) vs W.  
Mean age = 50 to 55.

Mortality did not differ between NOACs and W

All-cause mortality (RR = 0.97)

VTE mortality (RR = 1.00)

Recurrent VTE (RR = 0.95)

### 5. Adverse effects:

Compared with the VTE studies, the AF studies included older patients who may have had more chronic medical conditions, increasing the risk for adverse effects. Also, the treatment duration was longer.

Adverse effects NOACs vs W;

Fatal bleeding (DTI RR = 0.72; FXI RR = 0.55)

Major bleeding (DTI RR = 0.90; FXI RR = 0.75)

GI bleeding (DTI RR = 1.50; FXI RR = 1.14)

Discontinuation of study drug, and elevated liver enzymes did not differ

between groups. Across all studies, the risk for myocardial infarction did not differ from W, but was higher with dabigatran (RR = 1.35) than for FXI (RR = 0.84)

The rates of fatal bleeding were consistently lower with NOACs. Major bleeding was decreased with NOACs, but this effect varied across studies and was not explained by drug class. Risk for GI bleeding was increased with NOACs but variability was significant across studies and not explained by drug class.

This unexplained variability suggests the possibility of important differences between individual drugs, even within drug class.

Affected patients were typically over age 75, and had renal impairment.

The relative rates of drug discontinuation due to adverse effects varied substantially across studies. Dabigatran had a higher risk for discontinuation than FXI (RR = 1.67).

#### 6. FDA reports;

Adverse effects reported to the FDA—dabigatran and W ranked first and second among suspect drugs:

Dabigatran: 3781 reports of adverse effects attributed to dabigatran (2367 hemorrhages; 291 acute renal failure; 644 strokes; 542 deaths; and 15 cases of suspected liver failure. AE occurred more frequently in elderly patients (mean age 80) and in those with renal impairment.

Warfarin: 1100 adverse events in 2011, including 72 deaths.

Rivaroxaban: adverse events associated with discontinuation were higher than for W. (HR = 1.51)

## DISCUSSION

1. NOACs were superior to W for some clinical outcomes, including mortality, in patients with AF. They were similar to W for primary outcomes in patients with VTE.
2. The adverse effects of NOACs compared with W were generally consistent across treatment indications, but some effects varied by drug class (DTIs vs FXI). Discontinuations due to adverse effects and myocardial infarction were higher with dabigatran. The FDA has issued alerts of serious bleeding with dabigatran, mostly in older patients or those with renal impairment.
3. For dabigatran, the comparative effects on vascular outcomes were dependent, in

part, with the quality of W treatment. The advantages of dabigatran were greater at sites with poor INR control.

4. W and dabigatran showed similar outcomes in centers with good INR control.
5. The effects on bleeding are complex. Fatal bleeding was significantly lower with FXIs than for W, but not for dabigatran. In contrast, GI bleeding was increased in patients receiving NOACs vs W.
6. A recent study found that, in patients older than 75, the risk for major bleeding was significantly higher for dabigatran than for W. (5.1% vs 4.3%). Bleeding risk may be increased for dabigatran in older adults and in those with impaired renal function.
7. MI was increased with dabigatran compared with FXIs.
8. Guidelines suggest that patients already taking W and maintaining good INR control have little to gain by switching to dabigatran.
9. W has been used for decades. Its limitations are well known. W reduces the risk of stroke by 62% (compared with 19% with aspirin) in patients with chronic AF. (This is then most common indication for anticoagulation.)
10. For treatment of VTE, outcomes were similar for NOACs and W.
11. No study reported patient's experience with health-related quality-of-life. However, a recent systematic review found that, for most patients, W does not have important negative effects on quality-of-life.
12. An increased risk of MI with dabigatran is of concern, although the evidence for this finding is low.
13. Three recent publications of cost effectiveness of dabigatran compared with W found dabigatran to be cost-effective but not cost saving.
14. Follow-ups for NOACs are generally short-term. It is possible that additional adverse effects will emerge with more widespread and longer-duration use.
15. The relatively short-term follow-up, and the lack of direct head-to-head comparisons of individual NOACs are important limitations of NOACs
16. Dabigatran and FXIs have the advantage of more predictable anticoagulation, fewer drug interactions and equal or better mortality and vascular outcomes compared with W. But treatment benefits of NOACs (vs W) depend on the quality of INR monitoring.
17. Important unanswered questions include which patients are most likely to benefit,

which, if any, of the new drugs is most effective, and whether dose-adjustment is indicated for patients at higher risk of adverse effects.

## CONCLUSION

NOACs are a viable option for patients requiring long-term anticoagulation. Treatment benefits compared with W are small and depend on the control achieved by W.

Annals Internal Medicine December 4, 2012; 157: 796-807

A Systematic Review, first author Soheir S Adam. Duke University Medical Center, Durham NC'

Supported by the VA Office of Research and Development.

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*Dabigatran: Pradaxa (Boehringer Ingelheim)*

*Rivaroxaban: Xarelto (Bayer)*

*Apixaban: Eliquis (Pfizer)*

*This is a confusing array of observations. Obviously, we need more time and experience with these drugs, especially for long-term treatment of AF.*

*There are no direct comparisons between individual NOACs.*

*These are powerful and dangerous drugs. We need time to evaluate differences especially for individual dose, adverse effects, and length of treatment time.*

*The observation that NOACs should be used with caution in elderly patients and those with renal dysfunction. This would eliminate a host of patients.*

*I recently read that the FDA had approved apixaban for treatment of VTE.*

*Meanwhile most primary care clinicians, I believe, should stick with warfarin.*

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## **12-5 THE RISK OF HIP FRACTURE AFTER INITIATING ANTIHYPERTENSIVE DRUGS IN THE ELDERLY**

More than 50% of all adults over age 65 have hypertension. The likelihood of developing hypertension during an average lifespan is more than 90%. Over 70% of newly diagnosed hypertensive patients over age 60 take anti-hypertension drugs.



Initiating anti-hypertension drugs in elderly patients can potentially cause orthostatic hypo-tension with associated symptoms such as dizziness, faintness, or syncope. This effect is acute, occurs over a relatively short time, and may lead to falls and hip fractures.

Some studies indicate that initiation of drugs such as thiazide diuretics and angiotensin II blockers, can increase fall risk in the elderly. However, there is little information about the immediate increased risk of hip fractures during initiation of therapy.

This study examined the association between the initiation of anti-hypertension drugs and immediate risk of hip fracture in a large population of community-dwelling elderly persons.

## STUDY

1. A population-based case series used the Ontario Drug Benefit Program prescription data base to identify all hypertensive residents age 65 and older who filled a first prescription for a thiazide diuretic, angiotensin II blocker, ACE inhibitor, calcium channel blocker, or beta-blocker.
2. Excluded patients who may have had conditions other than hypertension for which these drugs may have been prescribed. Also excluded patients in long-term care homes.
3. Identified (by self-report) the first occurrence of a hip fracture from 2000 to 2009.
4. Estimated the relative incidence of hip fracture for each person in the high-risk period (45 days immediately following initiation of an anti-hypertension drug), compared with 2 control periods (periods of 90 days before starting treatment and 90 days after the first 45 days of treatment).
5. The analysis eliminated patients with concurrent use of other potential fall-causing drugs, such as psychotropic drugs, during the observation period.

## RESULTS

1. There were 301 591 newly treated elderly hypertensive patients (mean age 81; 81% female; 6% had previous hip fracture). All were living in the community.
2. There were 1463 hip fractures during the 10 year study period.
3. Those who started an anti-hypertension drug had a 43% increased risk of hip fracture in the first 45 days of treatment compared with the control periods.
4. Those with hip fractures were most commonly exposed to ACE inhibitors (30%).
5. The incident rate-ratio of hip fractures were generally consistent among the 5

different classes of drug. But only ACE and beta-blockers reached statistical significance.

6. Further subdivision of the post-exposure risk period into 0 to 14 days and 15 to 44 days indicated that elderly people who initiated any anti-hypertension drug for treatment of hypertension had a 54% increase in hip fracture during the 15 to 44 day period. This increased trend was observed for most drug classes except for thiazides. It was statistically significant for ACE and beta-blockers.
7. There was no difference in incidence of hip fracture according to 5-year age bands after age 65.
8. Association of any anti-hypertension drug

	No of hip fractures	Incident rate ratio
Risk period	143	1.43
Control period	600	1.00 (Reference)

## DISCUSSION

1. Most of the medical literature on the association of anti-hypertension drugs and fracture has focused on long exposure periods.
2. The results of this study (of hip fracture risk) are generally consistent with the results of previous observational studies using falls as an outcome.
3. In this study, use of any anti-hypertension drug was associated with increased risk of hip fracture during the first 45 days of treatment, especially in days 15 to 44.
4. These findings are somewhat similar to a recent (2011) study demonstrating increased risk of falls with initiation of thiazides and beta-blockers, but not with other drugs.
5. The risk of hypo-tension related to ACE inhibitors has been related to venodilation and venous pooling with a fall in cardiac output. Beta-blockers cause bradycardia and decrease cardiac output and also cause confusion, which may result in falls. Thiazides decrease plasma and extra cellular fluid volume.
6. This study was not able to determine an absolute risk reduction that would help determine the number needed to harm.

## CONCLUSION

Anti-hypertension drugs were associated with immediate increased hip fractures during the initiating of treatment for hypertensive community dwelling elderly patients.

Caution is advised when initiating these drugs in the elderly.

Archives Internal Medicine, December 1/24, 2012; 172: 1739-44 Original investigation, first author, Debra A Butt, Ellesmere Health Care Center, Scarborough, Ontario, Canada.

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*Not a strong study. Requires confirmation. The absolute numbers of fractures due to beginning medications is likely to be small, but any hip fracture that can be prevented is important.*

*I had not thought of this relationship before. I believe few primary care clinicians would think of beginning anti-hypertension therapy as a cause of falls and fractures.*

*I believe a general principle for initiating long-term drug therapy in the elderly (as opposed to short-term urgent therapy as with antibiotics) would be to start with half dose followed by a period of observation for effectiveness and adverse effects.*

*This is because so many elderly have decreased ability to degrade drugs because of decreased renal and liver dysfunction.*

*As a rule, drug treatment might be better started at half dose in patients with hypertension, dyslipidemia, osteoporosis, depression, anxiety, and other psychiatric disorders. Also when starting treatment with sleeping pills, estrogen and progesterone, and thyroxin.*

*Dose may be gradually increased under observation.*

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***Can Go Into Remission—Rarely And With Difficulty***

## **12-6 ASSOCIATION OF AN INTENSIVE LIFESTYLE INTERVENTION WITH REMISSION OF TYPE-2 DIABETES: Randomized, Controlled Trial**

Traditionally diabetes has been considered a progressive, incurable disease. This notion is supported by the strong association with genetics and family history, the high prevalence of microvascular complications, and the loss of beta-cell mass and function, frequently present at diagnosis.

Bariatric surgery suggests that some cases of diabetes in obese patients can be put in remission.

This trial examined the association of a long-term intensive lifestyle intervention with remission of type-2 diabetes (DM-2).

## STUDY

1. Randomized, controlled trial (2001-2004; last follow-up 2008) compared an intensive lifestyle intervention (ILI) with a diabetes support and education (DSE) control. The ILI included weekly group and individual counseling for 6 months followed by 2 sessions per month and regular refresher group follow-up in years 2 to 4.
2. Entered and followed 4503 US adults with DM-2 and a body mass index of 25 and higher. DM-2 was defined as a fasting plasma glucose of at least 126 mg/dL or HbA1c of at least 6.5%.
3. Main outcome—partial or complete remission of diabetes. Partial remission of diabetes was defined as a transition from meeting criteria for diabetes to a pre-diabetes level of glycemic (fasting plasma glucose 100-125, and HbA1c 5.7% to 6.4%) with no anti-hyperglycemic medication. Complete remission was a transition to full normalization of glucose (fasting < 100; HbA1c < 5.7%).
4. The study was primarily designed to examine the effect of weight loss on cardiovascular disease, but offered a unique opportunity to examine the effect on control and progression of DM-2.
5. Excluded patients with particularly high HbA1c (> 11%), BP > 160/100, or plasma triglycerides > 600.
6. All were able to perform a maximal graded exercise test and complete 2 weeks of diet and activity self-monitoring.
7. The ILI aimed to reduce total caloric intake to 1200 to 1800 kcal/d through reductions in total and saturated fat, and to increase physical activity to a total of 175 minutes per week.
8. During periods of weight loss, ILI participants who were taking any anti-hyperglycemic medications were asked to provide blood glucose measurement records so that the investigators could determine if reductions in the medications were needed.

## RESULTS

1. Baseline characteristics:	DSE (n = 2262)	ILI (n = 2241)
Age (mean)	59	58
Male %	41	41
Diabetes medications %		

None	7	7
Oral only	73	74
Insulin	19	19
Diabetes duration median Y	5	5
Body mass index (BMI)	36	36
HbA1c (mean)	7.4	7.3
Fasting plasma glucose	155	154
Fitness (METs)	7.2	7.2

- The sample was predominantly middle-aged, and of diverse race/ethnicity education level and medication status. None had undergone bariatric surgery.
- At year 1, participants in the ILI group lost more weight (-8.6% vs 0.7%) and at year 4 (-4.7% vs -0.8% %). And had greater increases in fitness at year 1 (21% vs 5.3%) and at year 4 (4.9% vs -1.5%).
- ILI participants were significantly more likely to experience remission (partial or complete) during the first year, then declining at year 4.
- Absolute prevalence of complete remission:

	Year 1	Year 4
ILI	1.3%	0.7%
DSE	0.1%	0.2%

- Among those who had a remission in the ILI group, about 1/3 returned to clinical diabetes status each year.
- Any remission during the first year was significantly associated with fewer years since diabetes diagnosis, lower BMI, lower baseline HbA1c, not taking insulin, a greater 1-year weight loss, and strong fitness improvement.

## DISCUSSION

- Complete remission was rare. Likelihood of remission was greater in the first year.
- Remission was notably higher in those with substantial weight loss, fitness improvement, shorter duration of diabetes, or lower HbA1c at entry.
- This study also considered cardiovascular effects of ILI. In 2012, after 8 to 11 years, the study was stopped by the sponsors when it was determined that ILI did not reduce occurrence of cardiovascular events.

4. Earlier intervention in the natural history of diabetes leads to better outcomes, perhaps because earlier in the natural history of diabetes, beta-cell function and mass is better preserved.
5. Bariatric surgery has been associated with substantially greater weight loss and greater rates of remission of diabetes than with this study.
6. The appropriate definition of diabetes remission remains ambiguous and debatable. It could be argued that the definition used in this study does not address the underlying health and function of beta-cells and cannot be used to define a cure for diabetes.
7. The study population was not ideal because half of the sample had at least 5 years of duration of diabetes, 19% were using insulin, and many had high HbA1c.
8. The study made no assessment of post-glucose challenge, beta-cell function or action of insulin to determine the mechanisms by which lifestyle interventions may lead toward remission and normalization of glycemic levels. There was no measure of insulin resistance. Some participants would likely still be classified as diabetic if an oral glucose tolerance test had been included.
9. These findings suggest that intensive lifestyle intervention may be associated with a partial remission of diabetes in a subset of patients with DM-2, particularly in those with diabetes of short duration, lower HbA1c levels, and who do not yet require insulin.

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*I abstracted this article to tell patients that their diabetes can go into remission under some circumstances. Patients cannot be told they may be cured of their diabetes. They will relapse if a strict program is not continued indefinitely.*

*The process is difficult and prolonged. It requires a high degree of support and time. It is not a very practical point for primary care. Patients simply cannot maintain such a long and difficult program.*

*Most patients will fail to conform to the program and thus lose any chance of success. Those undergoing bariatric surgery have no choice. Their course is determined and would be difficult to reverse.*

*I believe the benefit / harm –cost ratio of this intervention is low because the cost in time and effort is so high and the benefit small.*

*If a remission attempt is made, it should be made early after onset of diabetes.*

*Prevention is much better. It must also be started early while some beta-cell function remains and while cellular insulin resistance has not progressed to an irreversible state.*

*The primary purpose of this trial was to determine if such a strict program would reduce cardiovascular complications of diabetes (myocardial infarction, non-fatal stroke, angina, death). It did not.*

