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Richard T. James Jr. M.D.

Editor/Publisher.

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## *Caregivers Deserve More Attention From Clinicians.*

### **8-1 THE CRITICAL ROLE OF CAREGIVERS IN ACHIEVING PATIENT-CENTERED CARE**

Achieving high-quality cost-effective medical care is an elusive goal in the US.

There is widespread agreement that patient-centered care (PCC) will be a key ingredient.

For frail elderly and for patients with advanced illness, many with multiple chronic diseases, PCC is impossible without caregiver involvement.

The critical role of caregivers deserves more attention from clinicians.

Who depends on caregivers?

At any time, an estimated 42 million Americans serve as caregivers and, on average, spend 20 hours per week on caregiving—shopping, cooking, bathing, dressing, and other basic activities of daily living. Many caregivers report responsibility for complex medical tasks that often are the province of a professional nurse—wound care, treating pressure ulcers, administering medications and fluids, operating medical equipment, and preparing special diets. The majority of caregivers are middle aged women caring for aging parents.

Substantial disability characterizes the final years of life, necessitating caregiver involvement. Some elders have advanced organ failure and experience frequent exacerbations of illness. Many are frail and have dementia with limited ability for self-care.

If medical care is to be self-centered and reflect patients' values when the patient cannot articulate his values, clinicians must rely on surrogates for guidance. Yet, few programs caring for patients with dementia regularly incorporate caregivers in every phase of care. Most interventions involving caregivers focus on psychosocial support intended to decrease their burdens.

Frail patients often cannot carry out their wishes without significant assistance. Planning for them may involve direct involvement of caregivers to aid in following clinical practice guidelines and optimizing care of illness and transitional care to avoid readmission to hospital after discharge.

Few programs targeted to the chronically ill involve caregivers, although those that do have demonstrated beneficial effects on the quality of care.

Nurse practitioners may perform home-based geriatric assessments and educate caregivers. Guided care decreases costs and increases patient satisfaction.

What is the role of the caregiver?

The caregiver should understand the patient's underlying health status, the diagnosis, and prognosis for life expectancy and the expected trajectory over the coming months. The key to realistic decision making includes choices such as life-prolonging vs comfort-care oriented treatment . Understanding the vulnerability of a frail person in the setting of a new stressor is essential to making informed decisions about hospital vs home care.

Another step in achieving PCC is to elicit and prioritize goals of care. We increasingly recognize the importance of determining the patient's goals as a prelude to determine plans for future care. When offering a range of possible goals, many patients indicate that their paramount concern is maximizing quality of life, rather than prolonging life.

The patient's goals are the basis on which a plan of care should be constructed. Translating these goals into practice requires determining what interventions are appropriate.

Getting a plan of care also requires a comprehensive assessment of both the patient and the patient's surroundings. Whether the patient with advanced illness who develops pneumonia can be treated at home or will require hospitalization depends on the availability of a personal caregiver. The care plan should specify what the response should be when problems develop. Specifying exactly what should happen in all possible circumstances is impossible, but the plan should be sufficiently precise to guide the patient, caregiver, visiting nurse, ER physician and primary care physician.

Care plans need to be available across all sites of our complex care system. The most carefully thought-out plans of care will prove useless unless its details are transmitted across sites. Explicit communication of the plan is the best guarantee of success.

Implications for the health care system.

For caregivers to make patient-centered care a reality for frail elders and those with advanced illness, they will need unprecedented education and assistance.

The medical establishment needs to incorporate caregivers at every step of patient care. This will entail a fundamental shift from individual autonomy to family and caregiver-centered care.

**JAMA August 14, 2013; 310:575-76 "Viewpoint" by Muriel T Gillick, Harvard Pilgrim Health Care**

*Ongoing communication between all concerned is essential for good patient-centered care. Plan ahead. Hold frequent conversations. Get everyone on the same page. Know the patient's wishes (expressed at*

*present or in the past). An elderly patient's wishes may be impossible to follow. They may be unrealistic. This requires patience and continuing explanation. Keep the conversation and explanations going!*

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## **8-2 VASCULAR AND UPPER GASTROINTESTINAL EFFECTS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS: *Meta-analysis of individual participant data from randomized trials***

NSAIDs are among the most widely used drugs in the world, chiefly to treat pain. But their long-term use is limited by serious gastrointestinal adverse effects.

NSAIDs inhibit the two recognized forms of prostaglandin synthetase: cyclo-oxygenase-1 and cyclo-oxygenase-2 (COX-1 and COX-2). Since the analgesic and anti-inflammatory effects of NSAIDs are mediated by inhibition of COX-2 and the GI adverse effects are mediated by inhibition of COX-1, NSAIDs which selectively inhibit COX-2, leaving COX-1 intact, might reduce the risk of GI toxicity compared with other NSAIDs.

Several COX-2 selective inhibitory drugs (collectively known as coxibs) have been developed. Early trials comparing coxibs vs traditional NSAIDs seemed to confirm that coxibs had less GI toxicity. However, subsequent trials also showed unequivocally that coxibs were associated with increased risk of athero-thrombotic vascular events.

Subsequent trials indicated that some traditional NSAIDs might also have adverse athero-thrombotic effects, but these hazards might depend on the degree and duration of suppression of platelet COX-1. In these analyses, high-dose naproxen (500 mg twice a day), which induces near complete suppression of platelet thromboxane, did not seem to increase risk of athero-thrombosis, but other high-dose traditional NSAIDs regimens with only transient effects on platelet COX-1 were associated with small, but definite vascular hazard.

The FDA requires that summaries of characteristics of all NSAIDs carry a warning about risks of cardiovascular disease. The European Medicinal Committee decided that coxibs, but not traditional NSAIDs, should be contraindicated in patients with coronary heart disease or stroke, and used with caution in patients with risk factors for CHD.

The object of the present meta-analysis of individual participant data from randomized trials (The Coxib and Traditional NSAID Trials Collaboration) was to characterize and quantify the cardiovascular and GI risks of particular NSAID regimens among different types of participants, particularly those at increased risk of vascular disease.

## STUDY

1. Literature search found 280 trials of NSAIDs (including coxibs) vs placebo (n = 124 513 ) and 474 trials of one NSAID vs another NSAID (n = 229 296)
2. Main outcomes:
  - A. Major vascular events: non-fatal MI, coronary death, non-fatal stroke, stroke death.
  - B. Heart failure.
  - C. Upper GI bleeding
3. Drugs included the COX-2 inhibitors (coxibs): celecoxib, rofecoxib, etoricoxib, and lumiracoxib.

## RESULTS

| 1. Coxibs vs placebo  | Rate ratio |
|-----------------------|------------|
| Major vascular events | 1.37       |
| MI or coronary death  | 1.76       |
| Heart failure         | 2.28       |
| Upper GI bleeding     | 2.22       |

Major vascular events were increased by about one third by a coxib, chiefly due to an increase in major coronary events. Heart failure and upper GI bleeding were much more common in patients taking coxibs.

Compared with placebo, of 1000 patients allocated a coxib for one year, three more major vascular events occurred, one of which was fatal.

| 2. Ibuprofen vs placebo |      |
|-------------------------|------|
| Major vascular events   | 1.44 |
| MI or coronary death    | 2.22 |
| Heart failure           | 2.49 |
| Upper GI bleeding       | 3.63 |

Ibuprofen also significantly increased major coronary events (RR = 2.22) but not other major vascular events.

| 3. Naproxen vs placebo |      |
|------------------------|------|
| Major vascular events  | 0.93 |
| MI or coronary death   | 0.84 |
| Heart failure          | 1.87 |
| Upper GI bleeding      | 5.48 |

Naproxen did not significantly increase major vascular events.

Heart failure risk was roughly doubled by all traditional NSAIDs and coxibs.

All NSAID regimens (including coxibs) increased upper GI complications.

4. Excess risks were calculated for major vascular risks in patients with higher (2% per year) or lower (0.5%) risk. And for upper GI complications with moderate (0.5% per year risk vs those with lower risk (0.2% per year).

Annual excess risk of major vascular events

|           | High risk patients | Low risk patients |
|-----------|--------------------|-------------------|
| Coxibs    | 9                  | 2                 |
| Ibuprofen | 12                 | 2                 |
| Naproxen  | 0                  | 0                 |

Annual risk of upper GI bleeding

|           |    |   |
|-----------|----|---|
| Coxibs    | 4  | 2 |
| Ibuprofen | 15 | 6 |
| Naproxen  | 16 | 6 |

## DISCUSSION

1. Most of the information was derived from trials of 4 coxibs and high dose traditional NSAIDs. (Daily doses: ibuprofen 2400 mg, naproxen 1000 mg.)
2. Traditional NSAIDs and coxibs were associated with increased risk of cardiovascular disease and upper GI complications.
3. This meta-analysis showed that the vascular risks of ibuprofen are similar to coxibs, but that naproxen is not associated with an increase in major vascular events.
4. Overall, coxibs increased the risk of major vascular events by about a third.
5. Coxib added three major vascular events per 1000 persons per year, with one such event causing death.
6. Higher doses of ibuprofen also significantly increased risk of major coronary events.
7. Naproxen 500mg twice a day did not seem to increase the risk of major vascular events. This is consistent with experimental studies showing that this naproxen regimen is capable of producing COX-1 inhibition that is sufficiently prolonged and intense to result in platelet inhibition, which could attenuate any adverse vascular effects of COX-2 inhibition.
8. There was no evidence of any stroke risk of any NSAID studied.
9. All NSAIDs doubled the risk of heart failure causing hospital admission, consistent with this being a

COX-2 dependent hazard unrelated to variable platelet inhibition.

10. As expected, NSAIDs increased the risk of upper GI complications by about 2 to 4 times. Coxibs yielded the lowest risk of such complications, but risk was twice that of placebo.
11. There was clear evidence that NSAIDs increase the early risk of upper GI bleeding. Since the average trial duration was less than one year, this analysis does not provide reliable information about whether the risks of NSAIDs persist after prolonged treatment.
12. Overall, at the daily doses studied most frequently, the vascular risks of different coxib regimens seemed similar. Little information was available on whether the vascular hazards of coxibs were dose dependent, although there was a trend towards less risk with lower doses.
13. There was clear evidence that NSAIDs increased the early risk of upper GI complications.
14. Overall, at the daily doses studied most frequently (200 mg), the vascular risks of different coxibs seemed similar. There was a trend toward less risk with lower doses.
15. A key objective was to quantify the hazards of NSAIDs in patients with increased risk of vascular disease and GI complications. Excess risks were calculated for major vascular risks in patients with higher (2% per year) or lower (0.5%) risk. And for upper GI complications with moderate (0.5% per year risk) vs those with lower risk (0.2% per year).
16. Among those at low risk for vascular event (the majority of participants) the predicted absolute risks of major vascular events were small irrespective of the particular regimen chosen. For high risk patients (about 40% were taking aspirin) for every 1000 patients per year of a coxib, about 8 more would have a major vascular event, of which 2 would be fatal.
17. Naproxen might not be associated with increased risk of major vascular events. (This should be interpreted with caution.) Naproxen substantially increases risk of upper GI complications, which could be mitigated with proton pump inhibitors.
18. High dose naproxen seems to be associated with less vascular hazard.
19. This analysis indicates that the effects of treatment regimens in particular patients can be predicted, guiding decisions about clinical management of inflammatory disorders.

## CONCUSSION

The vascular risks of coxibs are comparable to high dose ibuprofen.

High dose naproxen is associated with less vascular risk than other NSAIDs.

Although NSAIDs increase vascular and GI risks, the size of these risks can be predicted, helping guide clinical decision-making.

Lancet August 31, 2013;382:768-79 Original investigation, by the Coxib and traditional NSAID Trialists' (CNT) Collaboration. Funded by the UK Medical Research Council and the British Heart Foundation.

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*The article included data about diclofenac. I omitted this.*

*These can be dangerous drugs. Use the lowest dose for the shortest time.*

*My choice would be naproxen plus a proton- inhibitor.*

*Risk of adverse events is increased because they are freely available over the counter. Clinicians may be unaware and have no control of them.*

*Risk of adverse effects is higher in those at risk for GI bleeding and those at higher risk of cardiovascular events. Caution especially in these groups.*

*Terminology and process are confusing. I attempted to clarify.*

*All coxibs, and ibuprofen increase risk of major vascular events. Naproxen is not.*

*All NSAIDs, including naproxen increase risk of heart failure and upper GI bleeding.*

*Older patients, who are more likely to use NSAIDS have higher risk of adverse effects, especially heart failure and kidney disease. They should understand the risks.*

### **8-3 THE AA-COX-PROSTAGLANDIN-THROMBOXANE PATHWAY**

*The terminology and process of formation of prostaglandins, and drugs that inhibit the process, are complex and confusing*

*With the help of Wikipedia, this is my attempt to clarify. (Subject to review and correction.)*

*The physiological process starts with arachidonic acid on which the cyclo-oxygenases act to form prostaglandins and thromboxane. Editor*

#### **1. ARACHIDONIC ACID (AA)**

AA is an omega-6 polyunsaturated fatty acid—the precursor of prostaglandins.

#### **2. CYCLO-OXYGENASE**

These enzymes convert AA to prostaglandins.

There are 2 cyclooxygenases—COX-1 and COX-2. Different tissues express varying levels of COX-1 and COX-2.

- A. COX-1 is a constitutive enzyme, found in most mammalian cells with a “housekeeping” role in many physiological processes. One effect is on the stomach lining, where prostaglandins produced by action of COX-1 serve a protective role
- B. COX-2 is undetectable in most tissues. It is an inducible enzyme, becoming abundant in activated macrophages and other cells at the site of inflammation. It promotes formation of prostaglandins, which cause fever, pain , and inflammation.

### 3. PROSTAGLANDINS

A group of lipid compounds derived enzymatically from AA by COX. They have important functions throughout the body.

Every prostaglandin contains 20 carbon atoms, including a 5-carbon ring.

They are mediators of a variety of physiological effects. They are not hormones, but autocrines (acting in the same cell from which it is synthesized) or paracrines (locally active). They act locally as messenger molecules. They differ from hormones in that they are not produced at a distant site, but locally in most tissues and organs throughout the body. Their target cells are present in their immediate vicinity. They are produced by almost all nucleated cells, and act on platelets, endothelium, uterus and mast cells.

### 4. THROMBOXANE

So named because of its role in clot formation. It is a vasoconstrictor and facilitates platelet aggregation, acting in the formation of blood clots. Circulating fibrinogen binds to aggregated platelets, strengthening the clot.

Thromboxane is formed in platelets from a prostaglandin derived from AA by action of COX-1. Thromboxane synthase, an enzyme found in platelets, converts the prostaglandin to thromboxane.

The method of secretion of thromboxane from platelets is still not clear.

Source: Wikipedia

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*Aspirin, even in low doses, irreversibly blocks formation of thromboxane in platelets by blocking action of COX-1, preventing formation of the prostaglandin precursor of thromboxane. High doses of naproxen also induce near complete suppression of thromboxane production and does not increase risk of major vascular events, myocardial infarction or coronary death. Ibuprofen, in contrast has only transient effects on platelet COX-1 and is associated with increased risk of major vascular events. (I do not understand this difference. Does ibuprofen not affect COX-1 in platelets? Can someone out there clarify this for me? Editor)*

## **8-4 DRUGS AFFECTING THE AA-CYCLO-OXYGENASE-PROSTAGLANDIN-THROMBOXANE PATHWAY AND THEIR ADVERSE EFFECTS**

### **1. NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)**

#### **A. Traditional NSAIDs:**

Traditional NSAIDs are not selective. They inhibit both cyclooxygenases (COX-1 and COX-2). This inhibits prostaglandins synthesis, reducing inflammation, pain, and fever.

These effects are mainly due to inhibition of COX-2

The most prominent traditional NSAIDs are:

aspirin

ibuprofen (*Aleve*)

naproxen (*Advil*)

All are available over-the-counter.

Aspirin is the only NSAID able to irreversibly inhibit COX-1. This inhibits formation of a prostaglandin in platelets, the precursor of thromboxane. Inhibiting formation of thromboxane reduces risk of arterial thrombosis.

(Acetaminophen is not considered an NSAID because it has little anti-inflammatory activity, It treats pain mainly by blocking COX-2 in the central nervous system. )

Most NSAIDs are non-selective inhibitors of both COX-1 and COX-2. The inhibition is completely reversible. They block the formation of prostaglandins. There is little difference in clinical efficacy among them when used at equivalent doses.

Adverse effects of traditional NSAIDs:

GI: With the widespread use of these drugs, adverse effects have become increasingly

prevalent. An estimated 10-20% of NSAID patients experience dyspepsia. The inhibition of COX-1 by traditional NSAIDs (blocking the gastric protective action of prostaglandins formed by COX-1) may cause GI ulceration and bleeding, especially aspirin (including enteric-coated aspirin). Some NSAIDs are acidic and may cause additional damage. Ulceration increases with longer use and higher doses. Use the lowest dose for the shortest time. Gastric irritation may be reduced by proton-pump inhibitors.

**Cardiovascular:** NSAIDs (aside from aspirin) and the new selective COX-2 inhibitors

increase risk of myocardial infarction and stroke. They are not recommended for patients who have had a previous heart attack. Naproxen seems less harmful in this respect. NSAIDs (aside from aspirin) are associated with a doubling risk of heart failure in patients with prior heart disease. Hospital admissions and deaths are increased.

**Renal:** NSAIDs are associated with a relatively high incidence of adverse renal effects

caused by changes in renal blood flow and perfusion pressure, which is ordinarily maintained by prostaglandins. Renal failure is especially a risk in patients who are also taking an ACE inhibitor (removing angiotensin II vasoconstrictive effect on the efferent arteriole), and a diuretic (which drops plasma volume and renal perfusion pressure)—a “triple whammy” effect. This adverse effect is especially important in patients with renal disease. Salt retention and hypertension may result.

**Photosensitivity:** Is a commonly overlooked adverse effect of many NSAIDs.

**Pregnancy:** NSAIDs are not recommended during pregnancy. They may cause premature

closure of the fetal ductus arteriosus and cause adverse effects on the fetal kidney. They are linked to miscarriage and premature birth. Acetaminophen is safer.

**Others:** Raised liver enzymes, headache, dizziness, are common. Hyperkalemia, confusion, bronchospasm, rash are less common. Erectile dysfunction has been reported.

**Drug interactions:** By reducing renal blood flow, NSAIDs may decrease efficacy of

diuretics. They may cause hypertension and antagonize effect of anti-hypertensives such as ACE inhibitors.

## B. Newer NSAIDs:

COX-2 inhibitors (coxibs; eg, celecoxib) selectively inhibit COX-2. Because COX-2 produces prostaglandins specific to inflammation, inhibition results in less pain, fever, and inflammation.

It was hoped that sparing COX-1 would preserve the prostaglandin which provides protection to the stomach mucosa. However, GI complications remain higher in patients taking coxibs.

This selectivity does not seem to negate other adverse effects of NSAIDs –increased risk of renal failure, thrombosis, and stroke.

Selective COX-2 inhibitors also increase the risk of athero-thrombosis, even with short-term use. High dose of some traditional NSAIDs (ibuprofen) are also associated with increased risk of vascular events.

Celecoxib (Celebrex: Pfizer) is an NSAID and selective COX-2 inhibitor. It is not available as a generic in the USA, only by prescription.

Source: Wikipedia

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*This is important because of the near universal use of NSAIDs and their lack of control by physicians. When a patient presents with unusual symptoms, knowing these adverse effects and suspecting their self-prescribed use, may lead to discontinuation, and benefit the patient.*

## *Lowers BP Compared With Usual Care.*

### **8-5 SELF-MEASURED BP MONITORING IN THE MANAGEMENT OF HYPERTENSION:**

#### *Systematic Review*

Clinical guidelines and the Joint National Committee recommend self-measurement of BP (SMBP) as an adjunct in management of hypertension. The AHA recommends SMBP for evaluation of patients with known or suspected hypertension to assess response to treatment and possibly improve adherence. .

However, it is not clear whether SMBP confers benefit, and if so, for how long and whether it needs to be combined with additional support.

This systematic review evaluated the effectiveness of SMBP with or without additional support.

#### STUDY

1. Included prospective comparative studies (n = 52) of SMBP with or without additional support.

Determination of BP had to be at the patients' home, either by the patient or by a companion. All varieties of SMBP monitors were included. Usual care included any protocol for clinic BP monitoring.

#### RESULTS

1. SMBP monitoring alone vs usual care:

Included 19 studies for change in BP. There was no statistically significant difference in BP at 2 months. At 6 months, there was a significant difference. (Mean difference = -3.9 / -2.4) At 12 months, the differences were no longer significant (-1.5 / -0.8)

The evidence for an improvement in BP using SMBP vs usual care is rated as modest-strength, and supports an improvement in BP with SMBP

2. SMBP monitoring plus additional support vs usual care.

Additional support included educational materials, letters to patients and providers on treatment recommendations, web resources, phone monitoring with electric transmission of BP, telecounseling, behavior management, medication management, nurse or pharmacist visits, calendar pill packs, and adherence contracts.

At 12 months, there was consistent benefit from the interventions compared with usual care. Five quality A studies reported a reduction of -2.1 / 0.0 to -8.3 / -4.4.

At 18 months, a single quality A trial showed no difference between groups, Two studies found statistically significant reduction of BP at 60 months.

Five studies reported a statistically significant higher proportion of patient achieved target. Two trials provided ambulatory BP, both favoring SMBP monitoring with additional support.

Compared with usual care, on the basis of consistent findings in quality A trials, high-strength evidence supports a reduction in BP using SMBP with some additional support

## DISCUSSION

1. In comparative studies, SMBP monitoring alone vs usual care provided moderate-strength evidence supporting a lower BP with SMBP monitoring at 6 months and possibly at 12 months.
2. For SMBP plus additional support vs usual care, high strength evidence supports a lower BP for up to 12 months.
3. The effect of SMBP beyond 12 months and the effect on clinical outcomes is uncertain.
4. The findings of this review are applicable to adults with uncomplicated hypertension without recent acute illness who are willing and able to participate in SMBP monitoring at home.
5. Despite the ostensibly similar research questions across studies, there was a large degree of variability in SMBP protocols, transmission of BP data, and types of additional support. It is not possible to draw firm conclusions about the potential effect of specific methods of additional support with SMBP monitoring.
6. The observed magnitude of BP reduction by SMBP monitoring would be clinically evident on a population level if sustained over time. A decrease of 2 or 5 systolic in the population is estimated to reduce mortality by 6% to 14% due to stroke, 4% to 9% due to heart failure, and 3% to 7% due to all causes.
7. In addition, SMBP may be beneficial by allowing physicians to avoid over-or under-treatment. SMBP may encourage patients to adhere to life-style modification.
8. SMBP and additional support are synergistic.

## CONCLUSION

SMBP monitoring with and without additional support lowers BP compared with usual care. The effect beyond 12 months and long-term clinical benefits are uncertain.

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Annals Internal Medicine August 6, 2013;159: 185-94 Original investigation, first author Katrin Uhlig, Tufts Medical Center, Boston Mass. Primary funding source: Agency for Healthcare Research and Quality

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*The investigators did a good job of herding these 52 cats.*

*There was little notice of ambulatory monitoring. Would this increase validity? Part of the value of SMBP lies in an increase in patient interest and compliance. Patients who are compliant with regular SMBP would be more compliant with the BP treatment regimen. To be effective, SMBP requires commitment. It must be continued long-term.*

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## **8-6 LONG-TERM SURVIVAL OF PARTICIPANTS IN THE PROSTATE CANCER PREVENTION TRIAL: *The Prostate Cancer Prevention Trial. (PCPT)***

With the advent of prostate-specific antigen (PSA) the rate of diagnosis of prostate cancer (PC) rose dramatically. Currently men in the US have a 16% lifetime risk of a diagnosis of PC. Over 240 000 cases were detected in 2012.

But, treatments for PC (radiation and surgery) are associated with a substantial risk of sexual, urinary, and bowel complications that affect the quality-of-life. Even active surveillance, the treatment of choice for many men with low risk PC, represents a substantial burden including adverse effects of biopsy, with occasional sepsis. Surveillance is costly and troublesome.

Another approach is PC prevention, which could be a meaningful public health intervention.

Finasteride (Proscar) inhibits reduction of testosterone to the more active form dihydro-testosterone. It was reported to increase the risk of high-grade PC. This led to abandonment of finasteride for PC prevention.

The present study is an observational follow-up on the original PCPT reported in 2003. It spans a total of 18 years since first randomization. It reports the number of PCs detected since inception of the study in 1992 and determined the overall survival rate after diagnosis of PC.

### **STUDY**

1. The PCPT was designed by investigators at the National Cancer Institute.

2. From 1994 through 1997, 18 882 men underwent randomization—finasteride vs placebo. Data collection continued until 2004, providing 10 years of continuous observation.
3. In 2005, a long-term observational follow-up study began in men in whom PC had been diagnosed during the trial to estimate PC mortality among men in the finasteride group compared with the placebo group.
4. The long-term follow-up was closed in 2009.
5. The primary endpoint was histologically confirmed PCs, which were graded by the Gleason score. A high-grade tumor was defined as Gleason of 7 to 10; a low-grade tumor 2 to 6.

## RESULTS

### 1. Diagnosis of PC:

In the original trial (1994-2003), 18 880 men were randomized to finasteride vs placebo. PC was diagnosed in 989 of 9423 (10.5%) the finasteride group and 1412 of 9457 (14.9%) in the placebo group. High grade PCs: 3.5% in the finasteride group and 3.0% in the placebo group.

Relative risk of PC in the finasteride vs placebo according to grade:

| PC grade   | Primary 2003 report | Current 18-year study |
|------------|---------------------|-----------------------|
| Any grade  | 0.75                | 0.70                  |
| Low grade  | 0.61                | 0.57                  |
| High grade | 1.27                | 1.17                  |

Finasteride was associated with overall lower risk of PC, especially low grade, but was associated with higher relative risk in high-grade PC.

### 2. Deaths:

A total of 5034 deaths was reported: 2538 in the finasteride group and 2490 in the placebo group.

#### A. 15-year overall survival estimate:

|             |        |
|-------------|--------|
| Finasteride | 78.0 % |
| Placebo     | 78.2 % |

The between group difference in the risk of death from high-grade disease was not significant.

#### B. Hazard ratio (adjusted) of death from any cause and death after PC diagnosis:

|                             |      |
|-----------------------------|------|
| Death from any cause        | HR   |
| Finasteride vs placebo      | 1.03 |
| Death after diagnosis of PC |      |
| Finasteride vs placebo      | 0.92 |

### High grade vs low grade PC

|                        |                 |
|------------------------|-----------------|
| High-grade finasteride | 1.00 (referent) |
| Low grade finasteride  | 0.64            |
| High grade placebo     | 0.90            |
| Low grade placebo      | 0.73            |

### C. Overall 10-year survival of men with PC according to cancer grade:

|                        | 10-year survival % (estimate) |
|------------------------|-------------------------------|
| Finasteride low grade  | 83%                           |
| Placebo low grade      | 81%                           |
| Finasteride high grade | 73%                           |
| Placebo high grade     | 73%                           |

## DISCUSSION

1. Although early detection of PC by means of PSA may lead to reduced mortality from the disease, it also leads to substantial over-diagnosis of cancer, most notably low grade PC. The risk of over-detection contributed greatly to the US Preventive Services Task Force recommendation against PSA screening.
2. The risk of low-grade PC appears to be significantly reduced by use of finasteride—a risk reduction of 38% in the original PCPT.
3. A major lingering concern was the observed increase in high-grade cancers in patients taking finasteride. In 2011, the FDA mandated revision of the drug label, stating that it might increase the risk of high-grade PC and it was not approved for prevention of PC. There was concern that the high-grade PCs among men receiving finasteride would be more aggressive and more lethal. If the increase in high-grade PC was a reflection of new high-grade cancers induced by finasteride, some increase in mortality among men receiving finasteride would become obvious during long-term follow-up.
4. This study, however, showed a reduced risk of PC in the finasteride group vs the placebo groups at 10 years. (10.5% vs 14.9%)
5. Although the number of high-grade PCs was higher in the finasteride group (333 vs 286), this 18-year follow-up found no increase in risk of death among men receiving finasteride. The 15-year survival in both placebo and finasteride groups was approximately 78%.
6. The cause of death in the majority was not available, and as a result PC-specific mortality could not be determined. But since the total number of high-grade cancers was small, with only a total of 177 deaths, there was not enough information to test non-inferiority.

7. Data from 18 years of follow-up showed that use of finasteride over a period of 7 years in a general population of men median age 63 at study entry reduced the risk of PC, but did not significantly reduce mortality. The reduction in risk was due to a relative reduction of 43% in low-grade PC among men receiving finasteride as compared with placebo. Although the prevention of these tumors did not appear to reduce overall mortality, increased diagnosis of PC is a problematic by-product of PSA testing in that treatment adds little, if any, benefit and that treatment causes considerable burden to the patient and to society.

## CONCLUSION

Finasteride reduced the risk of PC by about one third.

High grade PC was more common in the finasteride group.

After 18 years, of follow-up, there was no significant difference between finasteride and placebo in the rate of overall survival.

NEJM Ageist 15. 20-13; 369: 603-10 Original investigation, first author Ian M Thompson Jr. University of Texas Health Care Center, San Antonio, Texas

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*The article convinced me that finasteride is associated with an overall lowering of PC due to reduction of low-grade tumors.*

*Whether finasteride increases incidence of high-grade tumors remains undecided.*

*The investigation could not find any difference in mortality over 15 years between the finasteride and placebo groups. The authors state that, if the incidence of high grade tumors was increased, there should be an increase in mortality in this group. This was not evident.*

*Finasteride provides major benefits to men with benign prismatic hypertrophy. I believe most men with symptomatic BPH would choose to use the drug and accept any possible increase in tumor aggressiveness.*

*I recall the enthusiasm with which the PSA test was received when first introduced. It was considered a major advance in PC detection and therapy. .*

*How times have changed! Enthusiasm often morphs into disappointment in medicine.*

*Read the following commentary.*

*Most of the morbidity resulting from PC is a consequence of the diagnosis and management of the disease, rather than the disease itself.*

## **8-7 A ROLE OF FINASTERIDE IN THE PREVENTION OF PROSTATE CANCER**

*(This article comments on the preceding study.)*

All medical care should seek to achieve one or more of these goals: 1) relieve suffering, 2) prevent future suffering, 3) prolong life.

We should offer preventive services when science assures us that across the population we do more good than harm.

How should we know if a preventive service accomplishes one or more of these goals? All-cause mortality is the most appealing outcome in prevention trials because it clearly reflects the goal of prolonging life, and is not subject to the difficulties of accurately assessing a specific cause of death.

All clinicians who struggle with completing a death certificate can identify with the challenges in ascertaining the cause of death.

Most single diseases play a small role in overall mortality

Prostate cancer is a logical target for preventive service. Most of the public discourse about PC prevention is focused today on screening asymptomatic patients, with the hope of altering the natural history of the cancers that are destined to cause suffering, without doing much harm in the process.

Most of the morbidity resulting from PC is a consequence of the diagnosis and management of the disease, rather than the disease itself. Many screen-detected PCs would never become apparent in the lifetime of the patient in the absence of screening. In the judgment of the USPSTF, the benefit of screening for PC by PSA does not outweigh the harms.

The PCPT (2003) was a landmark study that sought to reduce the morbidity and mortality of PC with the use of finasteride to prevent the disease. Using the incidence of cancer as a proxy for morbidity and mortality, the trial found a significant reduction in PC among men receiving finasteride, but ultimately a small increase in the number of high-grade cancers.

The preceding study seeks to allay that concern by examining long-term all-cause mortality among PCPT participants. The results are reassuring, with the 15-year death of 22% in both the finasteride and the control groups. The investigators were unable to report the PC-specific mortality. A small difference in PC mortality can exist in the absence of a difference in all-cause mortality.

What can we now conclude about finasteride for prevention? The safest conclusion is that finasteride has no short- or long-term effect on all-cause mortality, so we cannot recommend finasteride use to prolong life.

What about the prevention of future suffering? In interpreting the study, it is important to note that both the finasteride and placebo groups were being actively screened for PC. For those who choose regular PC screening, the use of finasteride meaningfully reduced the risk of PC, and thus the morbidity associated with treatment of the disease.

Whether the drug has either a negative or positive effect on PC specific mortality remains unknown. But either way, the effect is probably very small and does not result in any difference in life expectancy.

Men who understand the benefits, risks, and uncertainties associated with the finasteride for prevention may make a rational decision to take the drug to reduce the harm of screening. Another way to reduce the harm of screening is to choose not to be screened.

NEJM August 15, 2013; 369-70 Editorial by Michael LeFevre, University of Missouri, Columbia.

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