favorable than would be predicted based on stage considerations. While poor pulmonary function and coexisting disease led to low resection rates among those with early-stage disease, 89% of deaths in the EG and 92% in the CG deaths were due to LC. There can be little doubt that poor survival in both groups was a direct consequence of low resectability.

These results provide powerful evidence that CXR screening does not lead to the overdiagnosis of LC. Indeed, the overdiagnosis hypothesis would appear to be the antithesis of all that is known about LC.

We live in the age of evidence-based medicine. However, we do not have a clear understanding of the nature of evidence when it comes to measuring the effect of our early detection interventions. We screen to exploit opportunities provided by lead time and length-biased sampling, yet we spuriously dismiss real benefits as reflecting lead time bias, length bias, or overdiagnosis bias. Proper interpretation of cancer early detection trials is exceedingly complex. However, the significant stage distribution, resectability, and long-term survival advantages reported in this new study, which confirm similar findings from RPTs, represent solid evidence that CXR screening can save lives. It is as simple as ABC.

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Reversal of the Anticoagulant Effects of Warfarin by Vitamin K₁

Vitamin K is a cofactor for the posttranslational carboxylation of glutamate residues to γ-carboxyglutamates on the N-terminal regions of vitamin K dependent proteins. The process of γ-carboxylation is necessary for the biologic activity of vitamin K-dependent clotting factors, because it is required for calcium dependent complexing of the clotting proteins to their cofactors on phospholipid surfaces. During the carboxylation reaction the reduced form of vitamin K (vitamin KH₂) is oxidized to vitamin K epoxide, which is recycled to vitamin K by vitamin K epoxide reductase, which in turn is reduced to vitamin KH₂ by vitamin K reductase (Fig 1).

Warfarin exerts its anticoagulant effect by inhibiting vitamin K epoxide reductase and to a lesser extent vitamin K reductase. This process leads to the depletion of vitamin KH₂ and as a result, limits the γ-carboxylation of the vitamin K-dependent coagulant proteins (prothrombin, factor VII, factor IX, and factor X) and the regulatory anticoagulant proteins (protein C and protein S).

The anticoagulant effect of warfarin can be overcome by vitamin K₁ (both dietary and medicinal) because this oxidized form of the vitamin can be reduced through a warfarin resistant vitamin K reductase enzyme system (Fig 1).

Dietary vitamin K₁ is obtained predominantly
Discontinuation of Warfarin Therapy

White and colleagues\(^9\) reported that it takes about 4 days for the INR to return to the normal range when warfarin is stopped in patients whose INR is between 2.0 and 3.0.

Use of Vitamin K\(_1\)

Vitamin K\(_1\) is available as an injectable solution, an oral solution, or as a tablet. It is able to reduce an elevated INR in anticoagulated patients within 24 h. Vitamin K\(_1\) may be indicated to lower the INR in anticoagulated patients in three different clinical circumstances. These are in patients: (1) with an elevated INR who are not bleeding, but are considered at increased risk, when it would be reasonable to reduce the INR to less than 5.0 within 24 h; (2) who require surgery, in which case it is reasonable to reduce the INR to 1.0 to 1.5 at the time of surgery; and (3) in those with serious bleeding, who should have their INR reduced to 1.0 as soon as possible.

Ideally, vitamin K\(_1\) should be administered in a dosage that rapidly reduces the INR into a safe range without: (1) exposing the patient to an unnecessary risk of thrombosis; (2) rendering the patient resistant to warfarin when it is restarted; and (3) exposing the patient to a risk of an anaphylactoid reaction.

The optimal dosage and the optimal route of administration of vitamin K have never been evaluated using a rigorous study design. Consequently, recommendations vary from doses ranging from less than 1 mg to up to 10 mg and all three routes of administration: intravenous, subcutaneous, and oral have been advocated.

High doses of vitamin K\(_1\) (≥10 mg) are effective but can lead to warfarin resistance for days after they are discontinued. The intravenous route is likely to give the most predictable response, but can be complicated by anaphylactoid reactions, and there is no definitive evidence that this rare, but serious complication can be avoided by using low doses intravenously.

The risk of over-correction and warfarin resistance can be reduced by using low doses of vitamin K\(_1\) and the risk of anaphylactoid reactions avoided by using the oral route of administration. A number of recent studies have confirmed older reports that both low doses of vitamin K\(_1\) and the oral route are effective.

The effectiveness of low-dose oral vitamin K\(_1\) was demonstrated in a randomized trial by Pengo and colleagues\(^{10}\) in 1993 who showed that 2.5 mg oral vitamin K\(_1\) was more effective than withholding

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1. KO - reductase - warfarin sensitive
2. K - reductase - warfarin sensitive
3. NADH dependent reductase - not affected by warfarin

**Figure 1.** Vitamin K\(_1\) is reduced to Vitamin KH\(_2\) by two warfarin-sensitive enzymes (KO-reductase to K-reductase) and the nicotinamide adenine dinucleotide dependent reductase system that is insensitive to warfarin.

From phylloquinone in plant material.\(^8\) Increased intake of dietary vitamin K sufficient to reduce the anticoagulant response to warfarin\(^7\) occurs in patients on weight reduction diets (rich in green vegetables) and those treated with intravenous nutritional fluid supplements rich in vitamin K.

**Therapeutic Vitamin K\(_1\) to Reduce the International Normalized Ratio in Anticoagulated Patients**

There is a strong relationship between the level of the international normalized ratio (INR) and the risk of bleeding. The risk of bleeding rises sharply when the INR exceeds 5.0, but the risk of bleeding is likely to be increased in high-risk patients (such as those having surgery) even when the INR is 1.5 to 2.0. If a patient has an elevated INR and is not bleeding or does not require surgery, then it is reasonable to reduce the INR to a safer level of <5.0 within 24 h. If the patient has serious bleeding the INR should be reduced to 1.0 as soon as possible. If the patient requires elective or urgent surgery it is reasonable to reduce the INR to 1.0 to 1.5 at the time of surgery.

Three approaches can be used to reduce the INR. The first, and least rapid, is to discontinue treatment, the second is to use vitamin K\(_1\), and the third and most rapid, is to transfuse the patient with fresh plasma or prothrombin concentrate. The choice of these approaches is based largely on clinical judgment since randomized trials using clinical end points have not been performed.
warfarin for correcting the INR to <5.0 at 24 h. More recently a number of cohort studies have been performed to identify an appropriate dose of oral vitamin K$_1$.

Crowther and colleagues$^{11}$ performed a prospective cohort study in 62 patients who were treated with warfarin and had INR values between 4.0 and 10.0. None of the patients had bleeding complications. The next dose of warfarin was omitted and 1.0 mg of oral vitamin K$_1$ was administered. The INR was lowered at 24 h in 59 of the 62 patients (95%); it was reduced to less than 4.0 in 53 (85%), to between 1.9 and 4.0 in 50% and to less than 1.9 in 22 patients (35%). None of the patients showed resistance to warfarin when oral anticoagulants were recommended. The results of this study suggest that 1 mg of oral vitamin K$_1$ can reverse a moderately elevated INR (4.0 to 10.0), within 24 h in most patients.

In a retrospective cohort study, Weibert and colleagues$^{12}$ evaluated the ability of 2.5 mg of oral vitamin K$_1$ to reverse an excessive warfarin effect in 81 patients with an INR of 5.0 to greater than 10.0. Ninety percent of the patients achieved an INR of less than 5.0 and only 17% developed an INR of less than 2.0. An INR of less than 5.0 was achieved in 48 h in all patients whose initial INR was less than 9.0. However, a dose of 2.5 mg of oral vitamin K$_1$ was suboptimal when the initial INR was >9.0, since it failed to lower the INR to <5.0 in 24 h in five of eight such patients (63%).

In this issue of CHEST (see page 1546), Wentzien and colleagues investigated a novel approach to lowering the INR in anticoagulated patients. In a prospective cohort study, they assessed the validity of a regression formula to predict the correct dose of vitamin K$_1$ in two groups of patients: (1) those who required reversal of their anticoagulant therapy because they required minor surgery; and (2) those whose INR was >5.0 and who were not bleeding. Oral vitamin K$_1$ was administered as a scored 5 mg tablet. Patients who required reversal of their INR prior to minor surgery or a dental procedure took vitamin K$_1$ 36 h before the procedure and continued their daily dose of warfarin: the aim was to reduce their INR to between 1.5 and 2.0. Patients whose INR was >5.0 held their dose of warfarin and received a dose of vitamin K$_1$ that was predicted (from the formula) to lower their INR into the targeted therapeutic range. There was a strong correlation between the actual and predicted change in the INR. The mean dose of oral vitamin K$_1$ for the first (preoperative) group was 5 mg and for the over-anticoagulated group it was 10 mg.

Taken together, the results of these studies indicate that oral vitamin K$_1$ is effective for reducing the INR in patients treated with warfarin. A dose of 1.0 to 2.5 mg is effective when the initial INR is between 5.0 and 9.0, but a larger oral dose (eg, 5 mg) is required when the INR is >9.0. A formula for vitamin K$_1$ dosage has been developed to aid in dosage selection, but as pointed out by the authors, the validity of their formulas should be confirmed by other laboratories using thromboplastins with different International Sensitivity Index values.

Since oral vitamin K$_1$ is effective for lowering the INR, it is the route of choice unless very rapid reversal of the INR is considered to be critical, in which case vitamin K$_1$ can be administered by slow intravenous infusion with or without supplementary plasma infusion.

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Rapid Vasomotor Effects of Estrogen

Men are Part of the Club

“We know of no culture that has said, articulately, that there is no difference between men and women except in the way they contribute to the creation of the next generation.”

Margaret Mead

Atherosclerotic coronary artery disease (CAD) is the leading cause of death for American men and women. Though the pathogenesis of CAD is multifactorial, recent work has identified endothelial dysfunction as an important early event in the atherosclerotic process. Endothelial dysfunction clinically is detected by a decrease in the normal vasodilatory response to acetylcholine (Ach) that results from partial or complete attenuation of the bioavailability of nitric oxide (NO). In the normal arterial wall, Ach stimulates endothelial cells to release NO, which induces vascular smooth muscle cell relaxation in a paracrine fashion. In the atherosclerotic vessel, the bioavailability of endothelium-dependent NO is lost, and Ach acts directly on vascular smooth muscle, causing “paradoxical” vasoconstriction. The same changes in vascular tone caused by Ach infusion are produced by a variety of stimuli (e.g., cold exposure, ischemia) in a variety of vascular beds, forming the basis for several clinically useful provocative tests of vascular function. Using such tests, endothelial dysfunction has been shown to occur in a number of clinical settings, including hypercholesterolemia, diabetes, hypertension, and cigarette smoking. Treatment of such risk factors is accompanied by detectable improvement in endothelial function.

Over the past decade, a large body of observational data has accumulated demonstrating that long-term treatment of postmenopausal women with estrogen (E2) reduces the incidence of CAD by 35 to 50%. Both long- and short-term E2 administration is associated with improved endothelial function in animal and human studies. Williams and colleagues first showed that brief (15 min) exposure to IV E2 improves endothelial function in cholesterol-fed ovariectomized female monkeys. These effects of E2 have since been documented in postmenopausal women by several groups of investigators. The observed rapid (ie, occurring over 15 to 20 min) vasodilatory effects of E2 in female animals and humans raise a number of interesting questions. One important question is whether E2 can stimulate this same rapid vasodilatory pathway in men as it does in women. An early study examining this question failed to demonstrate an acute effect of 17β-estradiol in men.' However, two more recent studies with larger patient populations demonstrate that IV administration of a mixture of conjugated equine estrogens improves the coronary response to Ach in men and to the cold pressor test in male cardiac allografts. In the current issue of CHEST (see page 1556), Reis and colleagues examine this issue further by demonstrating that a short exposure to conjugated equine estrogens also abolishes the abnormal coronary vasoconstrictor response to the cold pressor test in a group of 30 men, confirming the existence of the pathway for rapid E2-mediated vasodilation in men.

Intriguing mechanistic questions surround the observed rapid vasodilatory effects of E2. The cellular effects of E2 on gene expression occur over hours to days and are mediated by estrogen receptor-dependent effects on gene transcription. To date, two estrogen receptors (ER) are known, ERα and ERβ. These proteins, members of the larger family of steroid hormone receptors, act as ligand-activated transcription factors, and thus, alter gene transcription following binding of E2 to the receptor. Clearly, the rapid vasomotor effects of E2 such as those described by Reis and colleagues, occur too quickly to be mediated by this genomic mechanism. The nongenomic nature of the rapid effects of E2 is supported by in vitro studies demonstrating that gene transcription is not involved in the rapid vasodilatory effects of E2. How then, are these effects transduced? The following three likely explanations are presently being explored: (1) nonreceptor mediated effects such as direct effects of E2 on membrane function or ion channels; (2) effects mediated by a novel, as yet undescribed estrogen receptor; and (3) effects mediated by one or both of the classical ERs acting in a novel manner. Though some in vitro and in vivo data suggest receptor-independent effects of E2, these only occur with supraphysiologic concentrations of E2 and are