Tamoxifen for the Prevention of Myocardial Infarction in Humans: Preclinical and Early Clinical Evidence

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Tamoxifen is a member of the triphenylethylene class of drugs (Figure 1), originally derived from the estrogen-mimetic hydrocarbon stilbene. Like other members of the class (such as raloxifene, droloxifene, and toremifene), tamoxifen is dominantly an anti-estrogen: This is the mode of action that resulted in its widespread use for the treatment and prophylaxis of hormone-dependent cancers. More recently, however, it has become clear that its mode of action is more complex, with estrogen-like activities in some tissues and estrogen antagonist effects in others. This has led to the reclassification of this drug family as selective estrogen receptor modulators (or SERMs).4,5

Although the discovery of 2 isoforms of the estrogen receptor (one of the molecular targets of tamoxifen action), designated ER-α and ER-β, provided an attractive hypothesis to explain the differential effects of tamoxifen on different tissues, it remains difficult to rationalize the plethora of tamoxifen effects in terms of the expression patterns of estrogen receptor isoforms. In part, this may result from the use of terms such as “estrogen agonist activity” for physiological effects (such as lowering low-density lipoprotein [LDL] cholesterol), where tamoxifen mimics the effect of estrogen, even though it is unclear whether this effect of tamoxifen is mediated through the estrogen receptor or not.

More recently, tamoxifen and its analogues have been proposed for use in a wider range of diseases that might be affected by its pleiotropic effects, with particular focus on diseases where hormonal status is known to have an impact on incidence (such as osteoporosis and coronary heart disease [CHD]). Clinical trials with raloxifene (a SERM structurally related to tamoxifen) have demonstrated the ability of this class of drugs to reduce the risk of osteoporosis among postmenopausal women at high risk, and raloxifene is licensed for this indication. To date, however, the only studies of tamoxifen (or its analogues) on cardiovascular disease have come from secondary analyses of clinical trials among subjects (almost entirely women) at low absolute risk of myocardial infarction. The purpose of this article is to review the preclinical and clinical data on the use of tamoxifen analogues for the prevention of myocardial infarction.

Preclinical Data
Tamoxifen has been proposed to have cardiovascular benefits for a number of years, although the mechanism(s) contributing to that proposed protective effect are still contentious. These putative mechanisms can be classified into 4 groups: (1) effects on lipid metabolism, (2) antioxidant effects, (3) hormonal effects, and (4) antiinflammatory effects.

Tamoxifen lowers total plasma cholesterol concentration through at least 2, and possibly more, pathways: It is an inhibitor of sterol-Δ8,7-isomerase (SD8I), which prevents the conversion of zymosterol into cholesterol. It also affects cholesterol esterification by inhibiting ACAT. Both these effects may contribute, to differing degrees, to a lowering of total plasma cholesterol and LDL cholesterol in both experimental animals and in humans. In addition to these estrogen receptor–mediated effects, tamoxifen may increase apolipoprotein A-I biosynthesis in liver through estrogen receptor–independent effects, resulting in a relative increase in high-density lipoprotein compared with LDL (although the more powerful overall reduction in total cholesterol may dominate, resulting in a decline in the absolute levels of high-density lipoprotein cholesterol). Taken together, these effects result in a markedly beneficial improvement in the lipoprotein profile of individuals taking tamoxifen, which is qualitatively similar (although quantitatively somewhat smaller) than the effect seen with certain statins, such as simvastatin or pravastatin.

Tamoxifen also has weak antioxidant properties, protecting LDL cholesterol from potentially harmful oxidation, at least in vitro, which Wiseman suggested might contribute to the cardioprotective effect of tamoxifen. More recently, however, the value of antioxidant therapy in heart disease is widely disputed, and circumstantial evidence suggests that antioxidant activity is unlikely to be a major contributor to any cardioprotective effects of tamoxifen seen in humans.

Third, tamoxifen modulates the hormonal profile in both men and women, affecting pituitary gonadotrophin secretion (Figure 2), albeit in opposite directions. In postmenopausal women (the group most extensively studied), tamoxifen and its analogues consistently decrease gonadotrophin release (follicle-stimulating hormone [FSH], leuteinizing hormone,
and prolactin are all decreased. Investigation of the mechanism of action suggested that SERMs act directly as estrogen receptor agonists to mediate these effects on gonadotrophin secretion, as responsiveness to leuteinizing hormone–releasing hormone was increased rather than suppressed by chronic treatment with SERMs. Levels of estradiol (estradiol and estrone) as well as progesterone appear to be unaffected.

In marked contrast, tamoxifen and related anti-estrogens elevate gonadotrophins in men. FSH then acts on the Sertoli cells in the testes to stimulate testosterone production and also the transforming growth factor type β (TGF-β)–related cytokine inhibin-B. As a result, FSH, testosterone, and inhibin-B are all upregulated (by 20% to 50%) after treatment with tamoxifen. Because, again in men, the primary source of estradiol is through the action of aromatase on testosterone in extragonadal tissue, the levels of estradiol are also elevated by 20% or so. Levels of progesterone are unaffected. Although the mechanisms underlying the different responses to chronic anti-estrogen treatment in men and women have not been investigated, it is possible that the feedback inhibition of pituitary gonadotrophin release mediated by testosterone and inhibin-B in men but not women contributes to the differences observed.

The sex-specific responses of the pituitary gonadotrophins to chronic tamoxifen therapy make it difficult to predict whether the changes in hormonal profile might be beneficial or detrimental to the development of CHD. Premature menopause (a central hypoestrogenic state, associated with low FSH and leuteinizing hormone) increases risk of CHD substantially, but treatment with hormone replacement therapy does not reduce CHD risk. Considering hormonal status alone, therefore, it would be impossible to predict whether tamoxifen would have beneficial or adverse effects on CHD risk in women.

In contrast, in men, where any association of hormonal profile with development of CHD has been reported, it is almost always lower levels of testosterone and estradiol are associated with the development of CHD. Consequently, the impact of tamoxifen therapy on the hormonal profile of men with heart disease is likely to be toward normalization.

These substantial differences in hormonal responses to tamoxifen therapy between men and women suggest appropriate care must be taken before generalizing conclusions from studies of a single sex. However, the lack of any consistency in the relations between hormonal profiles, hormonal therapies, and cardiovascular risk does tentatively suggest that the effects of tamoxifen on the pituitary axis are not the major mechanism underlying its effects on the cardiovascular system.

Finally, we and others have shown that tamoxifen has an antiinflammatory effect both in humans and in experimental animals. Tamoxifen is likely to mediate these antiinflammatory effects, at least in part through the upregulation of the antiinflammatory cytokine TGF-β. This is the basis of the protective cytokine hypothesis, in which we proposed that TGF-β normally protects the vessel wall from proatherogenic changes and that reduced TGF-β activity promotes atherogenesis. This hypothesis has been confirmed in a range of experimental animals but remains untested in humans.

The antiinflammatory effects of tamoxifen include a marked reduction in C-reactive protein (CRP) levels, even at doses lower than those used to block estrogenic effects, as well as a reduction in levels of the acute phase reactant fibrinogen and alkaline phosphatase (a protein whose levels are often elevated in inflammatory conditions). The changes in CRP are especially interesting, as treatment with tamoxifen remains one of the few interventions that have successfully lowered CRP, an inflammatory marker prospectively associated with an increased risk of myocardial infarction. The mechanism is unknown, but because estrogen therapy increases CRP levels, the effect could be mediated by direct antagonism at the estrogen receptor.

Tamoxifen also has a number of effects on platelets. For example, it has been reported to have a strong hemodilution effect, reducing platelet counts. In contrast, tamoxifen actually increases production of reactive oxygen species by isolated platelets and so increases platelet function. It is therefore unclear whether the net effect of reduced platelet
rabbits and monkeys. In fat-fed cynomolgus monkeys, that remained had changed in phenotype displaying a more decreased by 30% compared with baseline, and the lesions formations, 1996). At the end of the study, lipid lesion area was Grainger, C. Witchell, and J. Metcalfe, unpublished observa-
tions, 1996). The extent of aortic lipid lesion development, detected by oil red O staining according to the Paigen strategy, is shown on the y-axis. After 24 weeks, the mice (groups of n = 8) were treated with 0.1 mg/kg per day or 1 mg/kg per day tamoxifen (TMX) through the oral route for a further 12 weeks. Not only was further lesion development suppressed, but the preexisting lesions regressed, containing less lipid and more fibrous tissue than before initia-
tion of tamoxifen treatment.

Irrespective of which of these many mechanistic pathways are dominant, the beneficial effect of tamoxifen in preclinical models of atherosclerosis is well demonstrated. We have treated 3 different mouse models of atherosclerosis with tamoxifen and demonstrated that irrespective of the genetic basis for susceptibility to vascular lipid lesion formation, treatment with tamoxifen at doses from 0.1 mg/kg per day (equivalent to a human dose of 5 to 10 mg/d) upward results in suppression of lesion formation. At doses of 1 mg/kg per day, lesion formation is all but abolished.33–35

Extending these studies, we have also shown that tamoxif en can reverse lipid lesion formation that has already occurred in apolipoprotein-E knockout mice. Mice were left for development of lesions until 24 weeks of age and were then treated with tamoxifen for a further 12 weeks (D. Grainger, C. Witchell, and J. Metcalfe, unpublished observations, 1996). At the end of the study, lipid lesion area was decreased by 30% compared with baseline, and the lesions that remained had changed in phenotype displaying a more cellular, matrix-rich, stable phenotype with virtually no inflammatory cell infiltrate (Figure 3).

Our findings in mice have been replicated by others in rabbits and monkeys. In fat-fed cynomolgus monkeys, Adams and colleagues43 found a 60% reduction in progression of atherosclerosis. The robust nature of these findings across species, in different laboratories, and with different experimental designs strongly suggest the findings are unaffected by factors such as age, gender, and diet, which commonly confound extrapolation of laboratory animal studies to the human population. Interestingly, however, 2 separate studies have now found that the related anti-estrogen raloxifene was ineffective at halting progression of atherosclerosis in animal models of atherosclerosis (including rabbits44 and monkeys45). The effect of raloxifene on mouse models of the disease has not yet been reported. The cause of this apparent difference between the convincing data obtained with tamoxifen and the negative data obtained with raloxifene is unknown but may ultimately be useful in shedding light on the major mechanistic pathways that contribute to the cardioprotective effects. However, this difference does highlight the need to select the triphenylethylene derivative to be used in clinical studies with care.

Clinical Research Studies

On the basis of the preclinical data and on the early reports that tamoxifen might have cardioprotective effects among women receiving tamoxifen as adjuvant therapy for breast cancer (see below), several clinical research studies have been carried out in which tamoxifen or related triphenylethylene derivatives have been given to individuals with heart disease and its impact on various end points (such as lipid profiles, inflammatory and clotting parameters, and endothe-

dial reactivity) have been assessed.

Clarke and colleagues46 demonstrated that treatment with tamoxifen for 56 days at 40 mg/d substantially increased endothelium-dependent flow-mediated dilation, a physiological measure of endothelial function. Tamoxifen treatment completely abolished the 3-fold difference in endothelial function between individuals with coronary artery disease and individuals with normal coronary arteries by angiography. This study also confirmed the changes in hormonal and lipid metabolism parameters noted above.

Once again, as in the animal models of atherosclerosis, the impact of the related SERM raloxifene on endothelial function is less clear cut than for tamoxifen. Griffiths and colleagues37 showed no effect of 60 mg/d raloxifene for 8 weeks on flow-mediated dilation, in direct contrast to the results of Clarke and colleagues46 using tamoxifen, whereas Sharouni et al48 reported improved flow-mediated dilatation on raloxifene treatment, although the magnitude of the effect was smaller than had previously been observed with tamoxifen.46

Like flow-mediated dilation, the intima-media thickness of the common carotid artery, measured by noninvasive ultrasoundography, is a commonly used surrogate marker for coro-

nary artery disease susceptibility. Simon and colleagues49 reported a significant reduction in intimal thickening among women treated with tamoxifen for at least 1 year. The extent of the reduction they observed was equivalent to more than 10 years of spontaneous evolution with aging, suggesting the effect was biologically as well as statistically significant.

Despite encouraging preclinical and early clinical research findings (based on surrogate end points) with tamoxifen, the real utility of this drug for the treatment of patients with coronary artery disease can only be determined by perform-
ing well-designed clinical trials, collecting hard end point data (such as hospitalization for myocardial infarction, or death from cardiovascular disease).

A number of such trials have already been conducted examining the impact of chronic tamoxifen use (from 2 to 5 years’ duration) on myocardial infarction (and other cardio-

vascular end points) in women with no preexisting disease. It is important to note that in each case, however, the studies

![Figure 3](http://circ.ahajournals.org/clip/fig3.jpg)

Figure 3. Impact of tamoxifen on established aortic lipid lesions in apolipoprotein-E–deficient mice (D. Grainger, C. Witchell, and J. Metcalfe, unpublished observations, 1996). The extent of aortic lipid lesion development, detected by oil red O staining according to the Paigen strategy, is shown on the y-axis. After 24 weeks, the mice (groups of n = 8) were treated with 0.1 mg/kg per day or 1 mg/kg per day tamoxifen (TMX) through the oral route for a further 12 weeks. Not only was further lesion development suppressed, but the preexisting lesions regressed, containing less lipid and more fibrous tissue than before initia-
tion of tamoxifen treatment.
were designed to examine the impact of tamoxifen treatment on breast cancer, and analyses designed to look at cardiovascular end points were a secondary aim of the studies. As a consequence, these studies only examine individuals at low risk of cardiovascular disease and in most cases had relatively few cardiovascular events to analyze as a consequence.

Despite these caveats, several of the larger studies have reported a significant reduction in myocardial infarction events among the tamoxifen-treated group. MacDonald and Stewart\(^\text{10}\) showed a 50% reduction in events in among women treated with 20 mg/d tamoxifen for 5 years, and subsequent studies have mostly reached similar conclusions.\(^\text{16,50,51}\) Although studies of tamoxifen use for the prevention (as opposed to treatment of breast cancer) have had negative outcomes.\(^\text{52,53}\) Interestingly, in a similar study design (the Multiple Outcomes of Raloxifene Evaluation [MORE]), raloxifene apparently had effects similar to those of tamoxifen, reducing cardiovascular events among women at higher risk of cardiovascular disease by 40% (relative risk, 0.60; 95% CI, 0.38 to 0.95), although no similar effect was seen in the whole cohort.\(^\text{9}\) Consequently, it seems likely that raloxifene does share some of the cardiovascular protective effects of tamoxifen, but is appears to be less powerful in both preclinical and clinical studies.

However, the available clinical evidence suggests that chronic tamoxifen use is not without risks. The increase in risk of endometrial cancer is well established (relative risk, 1.49; 95% CI, 1.16 to 1.90). Because the risk of endometrial cancer does not exist, the argument for tamoxifen use is therefore proportionately stronger. Tamoxifen use is also associated with a small increase in the incidence of gastrointestinal cancers (relative risk, 1.31; 95% CI, 1.01 to 1.69) but not in any other malignancies.\(^\text{54}\)

Of greater concern when considering tamoxifen therapy for cardiovascular disease is the increased incidence of pulmonary embolism (relative risk, 1.88; 95% CI, 1.88 to 3.01), which probably will affect both men and women (although all the data available to date are for women only).\(^\text{54}\) It is unclear what the mechanism behind this increase in risk for thromboembolism might be (although similar effects are seen with estrogens, such as hormone replacement therapy,\(^\text{57}\) but apparently not with raloxifene\(^\text{9}\)). Consequently, any trial designed to examine the effect of tamoxifen on myocardial infarction, particularly among individuals at high risk, will need to carefully consider the likely risk of increased thromboembolic complications, since these individuals may already exhibit a procoagulant phenotype.

The procoagulant effect of tamoxifen might also underlie the increase in stroke associated with tamoxifen use in women (relative risk, 1.49; 95% CI, 1.16 to 1.90).\(^\text{54}\) Because
of the relatively high incidence of cerebrovascular events among any population selected for high absolute risk of CHD (although particularly so among postmenopausal women), this perhaps represents the greatest concern when considering tamoxifen use for cardiovascular protection. In marked contrast, raloxifene actually reduced the incidence of cerebrovascular events in MORE, making the selection of the SERM most likely to be useful for cardiovascular treatment even more difficult; available evidence suggests that raloxifene may have weaker beneficial effects but an improved side effect profile.

Despite these risks, all the available data suggest that the risk-to-benefit ratio lies strongly in favor of benefit, particularly among populations at high absolute risk for myocardial infarction. Considering, for example, men with unstable angina and related acute coronary syndromes, the incidence of myocardial infarction is approximately 12% over a 6-month period, whereas the incidence of stroke is only 1.5% in the same population. If the impact of tamoxifen on inflammatory effects dominate, but direct hormonal effects may also participate.

Conclusions

A wealth of preclinical and clinical data now supports the hypothesis that tamoxifen exhibits powerful cardioprotective effects, although the mechanism(s) that contribute to the observed protective effects remain the subject of debate. It seems likely that a combination of lipid-lowering and antiinflammatory effects dominate, but direct hormonal effects may also participate.

Despite this evidence, a number of important questions remain to be answered: First, and most important, the bulk of the clinical data that is available relates to women at low absolute risk of myocardial infarction. If tamoxifen has similar effects on men at high risk (such as those presenting with unstable angina in whom the absolute risk of myocardial infarction may be as high as 30% in the following year), then real clinical benefit could ensue from the adoption of tamoxifen as a cardiovascular medicine. But are the current observations (largely on women with breast cancer) generalizable to men with heart disease?

Second, in the studies reported to date, the reduction in death from myocardial infarction after tamoxifen treatment is similar to that seen with statins. However, because the studies have been performed in women at low absolute disease risk, virtually none of the treated subjects were receiving statin therapy. It is possible, therefore, that tamoxifen and statins might not show additive benefit, particularly if the lipid-lowering effects of both drugs were central to their cardioprotective mechanism. The improvement in endothelial function reported after tamoxifen treatment, however, was observed among individuals who were receiving statin therapy.

Given the lack of any clear understanding of the biological mechanisms underlying the demonstrated cardioprotective effect of tamoxifen, answers to both of these important questions can only be obtained from further clinical studies. Studies currently underway (such as the Raloxifene Use for the Heart [RUTH] study) will only partly answer these questions, as only women are being enrolled. We believe that a clinical trial of tamoxifen treatment of men at high absolute risk of myocardial infarction despite current best therapy is justified on the basis of the available data, and a trial of this design is essential to determine whether this class of drugs really has any place in the cardiology medicine cabinet.

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