Upregulation of ventricular potassium channels by chronic tamoxifen treatment

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Aims
Tamoxifen is a selective oestrogen receptor modulator widely used in the prevention and treatment of breast cancer. Women receiving long-term tamoxifen therapy do not experience cardiac arrhythmias although acute perfusion of tamoxifen has been shown to inhibit cardiac $K^+$ currents. This observation suggests that chronic tamoxifen treatment does not negatively modulate cardiac $K^+$ currents. Therefore, we investigated the chronic effects of tamoxifen on $K^+$ currents and channels in mouse and guinea pig ventricles.

Methods and results
Female mice and guinea pigs were treated with placebo or tamoxifen pellets for 60 days. Voltage-clamp experiments showed that the density of the $Ca^{2+}$-independent transient outward ($I_{to}$), the ultrarapid delayed rectifier ($I_{Kur}$), the steady-state ($I_{ss}$), and the inward rectifier ($I_{K1}$) $K^+$ currents were increased in tamoxifen-treated mice ventricle. Western blot analysis revealed that protein expression of the underlying $K^+$ channels $Kv4.3$ ($I_{to}$), $Kv1.5$ ($I_{Kur}$), $Kv2.1$ ($I_{ss}$), and $Kir2.1$ ($I_{K1}$) were significantly higher in the ventricle of tamoxifen-treated mice. Protein expression of the $K^+$ channel subunits encoding $I_{Kc}$ and $I_{Kr}$ (ERG1, KCNQ1, and KCNE1) was also increased in tamoxifen-treated guinea pig ventricle.

Conclusion
Conditions with high oestrogen levels are associated with reduced $K^+$ currents. Thus, conceivably, tamoxifen might prevent the inhibitory effects of oestrogen on $K^+$ channels by blocking the oestrogen receptors, which would explain the reported increase in $K^+$ currents. These findings could contribute to explain the absence of cardiac arrhythmia with long-term tamoxifen therapy.

Keywords
Tamoxifen • Mouse • Guinea pig • $K^+$ currents • Oestrogen

1. Introduction
The selective oestrogen receptor modulator (SERM), tamoxifen, is commonly used in early and advanced hormone-responsive breast cancer. 1,2 It is well established that 5-year tamoxifen therapy is effective at reducing the death rate in pre- and post-menopausal breast cancer patients. 1,2 In addition, long-term tamoxifen treatment is also successfully used to reduce the incidence of breast cancer in high-risk women. 1,3–7

In large-scale clinical trials, reduction in cardiac morbidity was associated with long-term tamoxifen treatment. 8,9 However, concerns, regarding QT interval prolongation with tamoxifen treatment, have been raised by some clinical reports. 10,11 Lengthening of QT interval is the electrocardiographic manifestation of a prolongation of the cardiac action potential duration (APD), which is largely attributable to a reduction in $K^+$ channels. Excessive QT prolongation represents a significant risk factor for torsades de pointe and sudden cardiac death. Drug-induced torsades de pointe is a specific type of ventricular polymorphic tachycardia associated with prolongation of the QT interval.

Experimental studies have reported that acute exposure to tamoxifen could inhibit cardiac $K^+$ currents, 12–18 which would be consistent with QT prolongation. Based on these observations, tamoxifen has been classified as a drug that may prolong the QT interval although its lacks substantial evidence for causing torsades de pointe. Indeed, although tamoxifen acutely inhibits cardiac $K^+$ currents and may be related to QT prolongation, the drug has never been associated with the development of any types of cardiac arrhythmias.

The in vivo effects of tamoxifen are, at least in part, due to its active metabolite, 4-hydroxytamoxifen. In a recent study, we investigated the acute effects of 4-hydroxytamoxifen on cardiac $K^+$ currents in mouse. 19 We found that, as with tamoxifen, short-term exposure to 4-hydroxytamoxifen reduced $K^+$ currents in the mouse ventricle independently of the intracellular oestrogen receptor.

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So far, all the effects of tamoxifen and 4-hydroxytamoxifen on cardiac ion currents have been reported only after acute exposure to the drugs, which does not reflect the chronic conditions of the long-term tamoxifen therapy. Thus, it is plausible that the long-term effects of the drug on the ion currents may differ from those seen with acute perfusion of the myocytes with these drugs. Additional work studying long-term exposure to tamoxifen is required to elucidate this question. Furthermore, a large number of women who receive tamoxifen for extended period of time (i.e. 5 years) do not experience torsades de pointe. Accordingly, we hypothesized that chronic administration of tamoxifen does not reduce K+ currents in the heart. In order to test this hypothesis, in the present study, we examine the effects of chronic tamoxifen treatment on ventricular K+ currents and K+ channels in female mouse and guinea pig hearts.

2. Methods

All experiments were performed in accordance to the guidelines of the Canadian Council on Animal Care and the Guidelines for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996). Experiments were also approved by the Montreal Heart Institute animal care committee (approval reference number 2009–8002).

2.1 Tamoxifen treatment

Adul female CD-1 mice (2–3 months) and adult female guinea pigs (13–17 weeks) were anesthetized by inhalation of isoflurane. A 2–3 mm incision was made over the skin in the interscapular region. Control animals received a placebo pellet whereas the tamoxifen-treated animals received a tamoxifen pellet (5 mg/pellet, 60 day sustained release, SE-351, Innovative Research of America, Sarasota, FL, USA) implanted subcutaneously. This dosage regimen has been shown to inhibit both oestrogen receptor subtypes and evoke clinically relevant pharmacological concentrations of tamoxifen.20–22

2.2 Mouse ventricular myocyte isolation

Ventricular myocytes were isolated as previously described.23 After being heparinized and anesthetized with isoflurane, mice were sacrificed by electrophyresis and transferred to nitrocellulose membranes. Membranes were then incubated overnight at 4°C with rabbit polyclonal primary antibodies directed against the K+ channels studied. Ponceau S was used to confirm uniformity of the protein loading and transfer. Bands were quantified by densitometry using Multi-Analyst program (Bio-Rad, CA, USA).

2.5 Statistical analysis

Data were reported as mean ± standard error (SEM) and ‘n’ refers to the number of different cells. An unpaired Student’s t-test was used to compare mean data. P-values <0.05 were considered to be statistically significant.

3. Results

3.1 Chronic tamoxifen treatment increased the density of ventricular K+ currents

Adult female mice were treated with tamoxifen for 60 days to determine whether chronic tamoxifen treatment alters ventricular K+ currents. K+ currents were recorded from freshly isolated ventricular myocytes. To account for differences in cell size, all current amplitudes were normalized to the cell capacitance, and expressed as densities (pA/pF). Cell capacitances of ventricular myocytes isolated from control and tamoxifen mice was similar (control: 155 ± 7 pF, n = 11; tamoxifen: 137 ± 5 pF, n = 12). Figure 1A presents typical examples of a family of total K+ current (I_{K1}) recorded from control and tamoxifen-treated ventricular myocytes. Figure 1B summarizes the current–voltage (I–V) relationships of the peak currents for the two groups. This figure shows that the current density of I_{K1} measured at −110 mV was increased in tamoxifen-treated cells (−28.2 ± 7.8 pA/pF) compared with controls (−18.3 ± 7.4 pA/pF, P < 0.05). In addition, chronic tamoxifen treatment leads to an increase in the current density of the peak outward K+ current. As shown on Figure 1B, at +30 mV, there was a 38% increase in I_{peak} density in tamoxifen-treated cells (98.3 ± 5.3 pA/pF) when compared with controls (61.3 ± 4.5 pA/pF, P < 0.05).

3.1.1 Effect of tamoxifen on individual outward K+ currents

We then examined the effects of chronic tamoxifen treatment on the individual outward K+ currents contributing to I_{peak}. These K+ currents correspond to (i) the Ca2+-independent transient outward (I_{oCa}), (ii) the ultrarapid delayed rectifier (I_{KUR}), and (iii) the steady-state outward (I_{Kss}) K+ currents.24

3.1.1.1 The Ca2+-independent outward K+ current: I_{oCa}

Figure 1C shows representative I_{oCa} recordings from a control and a tamoxifen-treated myocytes. Figure 1D presents the corresponding mean I–V curves and illustrates that I_{oCa} was significantly larger in myocytes from tamoxifen-treated mice compared with control animals (at +30 mV, control: 30.8 ± 2.2 pA/pF, tamoxifen: 51.3 ± 1.9 pA/pF, P < 0.05).

3.1.1.2 The steady-state outward K+ current: I_{Kss}

Figure 2A and B compares the density of I_{Kss} in myocytes from control and tamoxifen-treated mice. As illustrated by the representative current traces (Figure 2A) and the mean I–V plots presented in Figure 2B, the density of I_{Kss} was significantly increased following chronic treatment with tamoxifen (at +30 mV, control: 15.0 ± 1.9 pA/pF, tamoxifen: 21.8 ± 2.3 pA/pF; P < 0.05). The increased
density of \( I_{K1} \) in the tamoxifen-treated group can also be appreciated in Figure 2A and B.

3.1.1.3 The ultrarapid delayed rectifier: \( I_{Kur} \)
Figure 2C presents superimposed current traces of \( I_{Kur} \) obtained in control and tamoxifen-treated cells. As illustrated in Figure 2D, which presents the mean \( I-V \) relationships for \( I_{Kur} \), there was also a significant increase in \( I_{Kur} \) density in ventricular myocytes from the tamoxifen-treated group (at +30 mV, control: 25.0 ± 2.6; tamoxifen: 39.8 ± 3.3 pA/pF, \( P < 0.05 \)).

3.2 Inactivation kinetics properties of the outward \( K^+ \) currents are not affected by chronic tamoxifen treatment

Currents produced by voltage-gated \( K^+ \) channels can often be described qualitatively by their kinetics of inactivation as well as their current–voltage relationships.27 Thus, understanding the inactivation parameters of repolarizing \( K^+ \) currents is crucial to establish the implication of these channels in repolarization.

3.2.1 Voltage-dependence of steady-state inactivation of \( I_{to} \) and \( I_{Kur} \)
Figure 3 shows the voltage-dependence of steady-state inactivation of \( I_{to} \) and \( I_{Kur} \) in control and tamoxifen-treated mouse ventricular myocytes. The steady-state inactivation of \( I_{to} \) and \( I_{Kur} \) was obtained using two-pulse protocols.24 The data were fitted to a Boltzman equation. The voltage dependence of steady-state inactivation of \( I_{to} \) was similar in control and tamoxifen-treated myocytes (\( V_{1/2} \), Control: -54.1 ± 0.7 mV and Tamoxifen: -57.2 ± 0.5 mV, \( P = 0.4 \); slope factor (k), Control: 6.5 ± 0.7 mV and Tamoxifen: 6.8 ± 0.5 mV; \( P = 0.5 \)) as illustrated in Figure 3A. Similarly, the voltage dependence of steady-state inactivation of \( I_{Kur} \) was comparable in control (\( V_{1/2} \): -48.1 ± 2 mV and k: 7.0 ± 0.3 mV) and tamoxifen myocytes (-50.8 ± 2 mV, \( P = 0.9 \) and k: 7.2 ± 0.4 mV, \( P = 0.9 \)) (Figure 3B).

3.2.2 Recovery from steady-state inactivation of \( I_{to} \) and \( I_{Kur} \)
Data describing the reactivation kinetics of \( I_{to} \) and \( I_{Kur} \) in control and tamoxifen-treated mouse myocytes are summarized in Figure 4. Data were fitted with a single exponential function. Figure 4A shows that the
time course of $I_{\text{to}}$ recovery from inactivation was comparable in myocytes isolated from tamoxifen-treated mice ($52 \pm 3$ ms) and control mice ($58 \pm 4$ ms, $P = 0.8$). Data presented in Figure 4B indicate that $I_{\text{to}}$ recovered from inactivation at a similar rate in control and tamoxifen-treated myocytes with a time constant of $803 \pm 66$ ms in control and $932 \pm 52$ ms, respectively ($P = 0.8$). Altogether, this suggests that the inactivation kinetics properties of both $I_{\text{to}}$ and $I_{\text{Kur}}$ were unaffected by chronic tamoxifen treatment.

### 3.3 Ventricular K$^+$ channel protein expression in tamoxifen-treated mice

The next set of experiments examined the protein expression of the K$^+$ channels corresponding to the mouse ventricular K$^+$ currents: Kv1.5 ($I_{\text{Kur}}$), Kv2.1 ($I_{\text{ss}}$), Kv4.2/ Kv4.3 ($I_{\text{to}}$), and Kir2.1 ($I_{\text{K1}}$). Since the accessory subunit, KChIP2b, can associate with Kv4.2 and Kv4.3 to increase the density of $I_{\text{to}}$, we also included KChIP2b in these western blot studies. Results of western blot analysis are presented in Figure 5A and B and show that Kv1.5, Kv4.3, Kv2.1, and Kir2.1 protein expression was significantly increased in the ventricles of tamoxifen-treated mice compared with the control animals. However, Kv4.2 and KChIP2b were unaffected by tamoxifen treatment.

### 3.4 Ventricular action potential duration in tamoxifen-treated mice

Since alterations in K$^+$ currents/channels can alter repolarization, we then compared APD in ventricular myocytes from control and tamoxifen-treated mice. Figure 5C presents mean APD measured at 90% of repolarization (APD$_{90}$) in control and tamoxifen-treated myocytes. Consistent with the increase in the density of the ventricular K$^+$ currents, the APD$_{90}$ was significantly shorter in tamoxifen-treated myocytes ($12.0 \pm 1.0$ ms) than that observed in controls ($24.4 \pm 0.6$ ms, $P = 1.8 \times 10^{-7}$).
3.5 Ventricular K\(^+\) channel protein expression in tamoxifen-treated guinea pigs

Although cardiac ion channels are highly conserved in mice and humans, significant differences are present in the repolarizing K\(^+\) currents between the two species.\(^{28}\) Specifically, human ventricular repolarization is strongly dependent on the rapid and slow components of the delayed rectifier potassium currents, \(I_{Kr}\) (carried by ERG1) and \(I_{Ks}\) (encoded by KCNQ1\(\alpha\) subunits and KCNE1\(\beta\) subunits).\(^ {29−31}\) However, these currents do not play an important role in the adult mouse ventricle. Therefore, to gain additional information on \(I_{Kr}\) and \(I_{Ks}\) potassium channel expression, in the last series of experiments we also examined the chronic effects of tamoxifen in guinea pig ventricle, which express functional \(I_{Kr}\) and \(I_{Ks}\) channels.\(^ {26,32}\)

Using western blot analysis, we compared the protein expression of ERG1, KCNQ1, and KCNE1 in ventricular tissues isolated from adult female guinea pigs chronically treated with either subcutaneous placebo or tamoxifen pellets. Figure 6A and B shows that ERG1 and KCNQ1 channels which correspond, respectively, to \(I_{Kr}\) and \(I_{Ks}\) \(\alpha\)-subunits were both significantly increased in the tamoxifen-treated guinea pig ventricles. In addition, KCNE1, the accessory protein of \(I_{Ks}\), was also significantly increased by tamoxifen.

4. Discussion

4.1 Summary of main findings

In this study, we demonstrated that chronic tamoxifen treatment significantly increases the density of \(I_{to}\), \(I_{Kur}\), \(I_{ss}\), and \(I_{K1}\) in adult female mouse ventricular myocytes. This increased K\(^+\) current density was accompanied by higher protein expression of underlying K\(^+\) channels (Kv4.3, Kv1.5, Kv2.1, and Kir2.1, respectively). Voltage-dependence and inactivation kinetics properties of the currents were unaffected by long-term tamoxifen exposure. These findings provide convincing evidence that long-term tamoxifen treatment does not negatively modulate K\(^+\) currents but, in the contrary, increases the current density of these channels.
density and protein expression of several ventricular K\(^+\) channels in the mouse heart. In addition, data obtained in guinea pig ventricles showed that the upregulation of the cardiac K\(^+\) channels produced by chronic tamoxifen treatment is not specific to the mouse heart but also applies to I\(_{\text{Kr}}\) and I\(_{\text{Ks}}\) K\(^+\) channel isoforms (ERG1 and KCNQ1-KCNE1), which also play a major role in human ventricular repolarization. Altogether this study demonstrates that long-term exposure to tamoxifen, a SERM, increases the expression of several cardiac K\(^+\) channel proteins. These findings strongly suggest that tamoxifen action is mediated by blockade of nuclear oestrogen receptors.

Previous experimental studies have shown that acute exposure to tamoxifen and its active metabolite 4-hydroxytamoxifen decreased cardiac ion currents by direct effects to the channels.\(^{14,19}\) For instance, we previously reported that the inhibition of cardiac K\(^+\) currents by 4-hydroxytamoxifen was observed even in the presence of the selective oestrogen receptor antagonist, ICI-182,780, or the inhibitor of RNA synthesis, actinomycin D.\(^{19}\) Similarly, the inhibitory effects of another SERM raloxifene on I\(_{\text{to}}\) and I\(_{\text{Kur}}\) in human atrial myocytes were unaffected by the oestrogen receptor antagonist ICI 182,780.\(^{13}\) These data indicate that the reduction in the repolarizing potassium currents following acute exposure to 4-hydroxytamoxifen or raloxifene was not mediated by the oestrogen receptors.

Thus, although acute exposure to tamoxifen or 4-hydroxytamoxifen inhibits cardiac K\(^+\) currents, it appears that other mechanisms take place with long-term tamoxifen treatment. Indeed, unlike the results obtained in acute studies, here we show that long-term tamoxifen treatment significantly increases the density of several cardiac K\(^+\) current paralleled with an upregulation of the protein expression of corresponding K\(^+\) channel isoforms. These differences may be explained by the fact that multiple sites of action are probably involved in the effects of tamoxifen on cardiac K\(^+\) channels, with an acute inhibitory effect mediated by direct and rapid actions on the K\(^+\) channels and a slower effect mediated through interactions with the oestrogen receptors that would be responsible for the increased density of the currents reported here.

Conditions with high level of oestrogen such as late pregnancy have been associated with reduced K\(^+\) currents both in the heart and the
**Figure 5** (A and B). Ventricular protein expression of $K^+$ channels in control and tamoxifen-treated mice. (A) Examples of western blots of Kv1.5, Kv4.2, Kv4.3, KChIP2b, Kv2.1, and Kir2.1 on sarcolemmal-enriched proteins (100 μg/lane) isolated from control and tamoxifen-treated mice. (B) Bar graphs comparing the relative protein expression of the different $K^+$ channel isoforms between the two groups show that protein expression of Kv1.5, Kv4.3, Kv2.1, and Kir2.1 are markedly increased after chronic tamoxifen treatment. Relative abundance was calculated with value for control mice as a reference of 1 (*$P < 0.05$ vs. Control; $n =$ 3/group; 2 hearts/sample). (C) Shortening of APD with chronic tamoxifen treatment. Bar graphs comparing mean APD$_{90}$ recorded in ventricular myocytes from control ($n =$ 10) and tamoxifen-treated mice ($n =$ 11) at a rate of 4 Hz (*$P < 0.05$ vs. Control).

**Figure 6** $K^+$ channel protein expression in control and tamoxifen-treated guinea pig ventricles. (A) Examples of western blots of ERG1, KCNQ1, and KCNE1 on sarcolemmal-enriched proteins (100 μg/lane) from control and tamoxifen-treated guinea pig ventricles reveal a significant increase in ERG1, KCNQ1 and KCNE1 protein expression with chronic tamoxifen treatment. (B) Bar graphs comparing relative abundance of ERG1, KCNQ1, and KCNE1 protein expression determined by densitometry. Relative abundance was calculated with value for control guinea pigs as a reference of 1 (*$P < 0.05$ vs. control; $n =$ 3/group; 1 heart/sample).
Chronic tamoxifen increases cardiac $K^+$ channels

uteros. Eghbali et al.\textsuperscript{34} reported that at the end of pregnancy, cardiac $I_o$ as well as Kv4.3 channel gene expression was downregulated. In addition, they showed that downregulation of cardiac Kv4.3 transcripts was mimicked by oestrogen treatment in ovariectomized mice, and was prevented by the oestrogen receptor antagonist ICI 182,780. Similar findings have also been reported in rat myometrium where Kv4.3 expression was downregulated during pregnancy and following oestrogen treatment.\textsuperscript{35} In line with these findings, recently Saito et al.\textsuperscript{36} reported that ovariectomy increased whereas oestrogen decreased the density of K\textsuperscript{+} currents/channels ($I_o$/$K_v4.3$ and $I_{K_{arb}}$/Kv1.5) in the mouse ventricle. Altogether, these studies are consistent with the results reported here where we show that inhibition of the oestrogen receptors following long-term exposure to tamoxifen leads to a significant increase in cardiac K\textsuperscript{+} current associated with upregulation of the underlying K\textsuperscript{+} channel expression. Thus, it is conceivable that tamoxifen prevents the oestrogen inhibitory effects on K\textsuperscript{+} channels by blocking the oestrogen receptors. This would explain the increased density of the cardiac K\textsuperscript{+} currents and channels observed in this study. Furthermore, we also examined that effects of tamoxifen on ovariectomized mice and found comparable results as those obtained in the intact females (data not shown). These findings suggest that the tamoxifen effects on oestrogen receptors are mediated independently of the oestrogen level.

The K\textsuperscript{+} channel isoforms Kv4.2 and Kv4.3 correspond to the murine ventricular $I_o$.\textsuperscript{24,37–41} We previously reported that overexpression of the $\alpha_{1B}$adrenergic receptor\textsuperscript{42} or the human type 1 angiotensin II receptor\textsuperscript{43} in the mouse heart is associated with a parallel reduction in ventricular Kv4.2 and $I_o$ density without any difference in Kv4.3 expression. In contrast, here we show a corresponding increase in $I_o$ and Kv4.3 with chronic tamoxifen treatment while Kv4.2 protein expression was unaffected. Interestingly, similar to what is reported here, work realized using pregnant or oestrogen-treated animals also showed that a specific reduction in Kv4.3 was responsible for the lower density of $I_o$.\textsuperscript{34} It is noteworthy that a specific reduction in Kv4.2 or Kv4.3 produces a parallel effect on the density of $I_o$. However, the reason why under different pathological or physiological conditions only Kv4.2 or Kv4.3 isoform is affected is intriguing and warrants further investigations.

Thus far, the inhibition of cardiac K\textsuperscript{+} current has been reported only after acute exposure to tamoxifen. Furthermore, even though clinical trials have documented QT prolongation with the use of the drug, it is important to note that tamoxifen has never been associated with the development of torsades de pointe. Therefore, it is reasonable to think that the QT prolongation reported in some clinical studies might not be directly associated with tamoxifen and that other factors could have been at the origin of the ECG abnormalities. Results presented here are in support of this view.

4.2 Limitations of the study

Although the data reported here strongly support the hypothesis that the observed effects of chronic tamoxifen are mediated by the blockade of oestrogen receptor, we cannot exclude the possibility that our findings could also be due to other unknown actions of tamoxifen. However, in the course of a separate study, oestrogen receptor deficient mice $\alpha$ (ERKO\textsubscript{\alpha}) and $\beta$ (ERKO\textsubscript{\beta}) were used to investigate the roles of oestrogen receptors on repolarization. Preliminary data show that Kv4.3 protein expression was increased in ERKO\textsubscript{\alpha} and ERKO\textsubscript{\beta} mice compared with wild-type mice.\textsuperscript{44} Thus, these data further support our conclusion that inhibition of oestrogen receptor

is responsible for the increased K\textsuperscript{+} current densities and their corresponding channel proteins during chronic tamoxifen treatment. Taken together, our findings strongly suggest that oestrogen receptors are involved in regulation of ventricular repolarization.

Because of the differences in repolarizing K\textsuperscript{+} currents between mouse and human ventricles, direct extrapolation of our findings to human repolarization remains uncertain. However, our studies reveal that long-term tamoxifen treatment also upregulates K\textsuperscript{+} channels in guinea pig, which expressed functional $I_o$ and $I_{K_{arb}}$ K\textsuperscript{+} channels (ERG1 and KCNQ1-KCNE1). These K\textsuperscript{+} channels are critical in human repolarization.

4.3 Conclusion

This study clearly establishes that long-term tamoxifen treatment significantly increases the density of several cardiac K\textsuperscript{+} currents paralleled with an upregulation of the protein expression of their corresponding K\textsuperscript{+} channel isoforms. This work provides new insight into the basic mechanisms of action of tamoxifen on cardiac electrophysiology and strongly suggests that there is an association between oestrogen, oestrogen receptors and the density of K\textsuperscript{+} channels in ventricular myocytes. Findings reported here could contribute to explain the absence of cardiac arrhythmias with the long-term use of tamoxifen therapy in breast cancer patients.

Supplementary material

Supplementary material is available at Cardiovascular Research online.

Conflict of interest: none declared.

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