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# Atrial Fibrillation is Associated With Morphine Treatment in Female Breast Cancer Patients

## A Retrospective Population-Based Time-Dependent Cohort Study

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**Abstract:** We investigated the relationship between morphine treatment and the risk of atrial fibrillation (AF) in female patients with breast cancer.

We identified a malignancy cohort of 73,917 female breast cancer patients without an AF history before the date of breast cancer diagnosis between 2000 and 2010 by using the Longitudinal Health Insurance Database for Catastrophic Illness Patients in Taiwan. This malignancy cohort was divided into morphine and comparison cohorts comprising 18,671 and 55,246 patients, respectively, and the incidences of newly diagnosed AF were calculated. We used the Cox proportional hazard model with time-dependent exposure covariates to estimate the risk of AF. The effect of morphine was assessed through multivariable Cox proportional hazard regression controlling for age, the Charlson comorbidity index (CCI) score, and the use of bisphosphonates and paclitaxel.

Compared with nonmorphine users, patients who received morphine exhibited a 4.37-fold (95% CI = 3.56–5.36) increase in the risk of developing AF. The risk of AF increased as the CCI score increased, but decreased in patients with tamoxifen treatment. This risk is especially significant in current morphine users of all ages and with low CCI score. AF risk increased as the duration of morphine use lengthened (*P* for trend <0.0001).

The incidence of AF in female breast cancer patients in Taiwan is associated with morphine, but prevented by tamoxifen treatment.

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**Abbreviations**: AF = atrial fibrillation, aHR = adjusted hazard ratio, BNHI = Bureau of National Health Insurance, CI = confidence interval, LHID 2000 = Longitudinal Health Insurance Database 2000, NHI = National Health Insurance, NHIA = National Health Insurance Administration, NHIRD = National Health Insurance Research Database, NHRI = National Health Research Institutes.

## INTRODUCTION

Atrial fibrillation (AF), characterized by disorganized electrical signals disrupting cardiac function, is the most common heart arrhythmia.[1,2] AF is highly prevalent in the elderly population and associated with congestive heart failure and thromboembolic mortality and morbidity as well as cognitive decline.[3–5] In the United States and Europe, the overall prevalence of AF is approximately 2% and the number of people affected has doubled over the past 2 decades.[6–8] In a Chinese community-based prospective cohort study in Taiwan, the overall prevalence of AF was 1.07%, and AF was a significant risk factor for stroke and all-cause death.[9]

Approximately 30% to 50% of cancer patients experience moderate-to-severe pain.[10] Oral morphine remains the analgesic of choice for moderate and severe cancer pain.[11] However, morphine induced AF in unanesthetized rats,[12] and AF was observed in acutely overdosed heroin addicts.[13,14] A recent analysis showed that opioid use was independently associated with an increased prevalence of AF.[15] Moreover, more Asian AF patients exhibit a history of previous stroke than non-Asian patients.[16] In our previous study, we determined that morphine was associated with an increased stroke incidence in cancer patients.[17]

Cancer patients are often administered morphine for pain alleviation; therefore, understanding the relationship between morphine use and AF incidence is crucial. To evaluate the potential for morphine-related AF, we compared the incidence of AF in female patients with breast cancer treated with and without morphine by using data from the Longitudinal Health Insurance Database for Catastrophic Illness Patients (LHID-CIP) of Taiwan.

# METHODS

## Data Source

We obtained access to the LHID-CIP from the Taiwan National Health Research Institutes (TNHRI). The TNHRI was commissioned to construct and maintain the National Health Insurance Research Database by the Taiwan National Health Insurance (TNHI) program, Bureau of National Health Insurance. The coverage rate of the TNHI program is over 99%. The LHID-CIP contains all inpatient and outpatient records for every catastrophic illness patient from 1997 to 2011. According to the Personal Information Protection Act, insurance information that can be used to determine patient identity is recoded, and all researchers had to sign an agreement stating that they had no intention to obtain personal information. This study was approved to fulfill the condition for exemption by the Institutional Review Board of China Medical University (CMUH104-REC2-115). The Institutional Review Board also specifically waived the consent requirement. In the LHID-CIP, diseases were coded according to the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM).

## Study Patients

We identified all patients with breast cancer (ICD-9-CM 174) between 2000 and 2010 from the LHID-CIP, and the date for breast cancer diagnosis was defined as the index date. The exclusion criteria were the following: receipt of morphine before the index date; a history of another malignancy (ICD-9-CM 140-173 and 176-208); a history of AF (ICD-9-CM 427.31); and metastasis development during the follow-up duration (ICD-9-CM 196-199). All patients were divided into 2 groups based on morphine treatment during the follow-up duration. The details of the study patients are presented in Figure 1.

## Endpoint, Comorbidity, Charlson Comorbidity Index Score, and Pharmacy

All study patients were followed from the index date to the date of AF onset. Those without AF development were followed until the date of withdrawal from the NHI program or the end of



**FIGURE 1.** The details of the study patients' selection.

2011. Baseline comorbidity included hypertension (ICD-9-CM 401-405), valvular heart disease (ICD-9-CM 424), hyperlipidemia (ICD-9-CM 272), hypothyroidism (ICD-9-CM 243 and 244), and hyperthyroidism (ICD-9-CM 242). The baseline Charlson comorbidity index (CCI) score was calculated according to a previous study[18,19]; patients with myocardial infarct, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, connective tissue disease, ulcer disease, mild liver disease, and diabetes received the score 1; those with hemiplegia, moderate or severe renal disease, or diabetes with end organ damage received the score 2; those with moderate or severe liver disease received the score 3; and those with AIDS received the score 6. All items of the CCI were defined in the inpatient claims. Pharmacy included bisphosphonates, paclitaxel, and tamoxifen. Patients received pharmacy treatment during the study period was defined users.

## Statistical Analysis

The differences in age group (age: <50, 50–64, and ≥65 years) and CCI score level (score: 0, 1–2, and ≥3) between the patients with and those without morphine treatment were assessed using a $\chi^2$ test. A *t* test was used to test the difference in mean age between the patients with and those without morphine treatment. Because patients with breast cancer may not have taken pharmacy regularly during the study period and this may lead to an overestimation of the effect of the drug, we used the Cox proportional hazard model with time-dependent exposure covariates to estimate the risk of AF to reduce this bias. The model enabled controlling the adjustments with a significant difference in crude Cox proportional regression. Thyroid dysfunctions, including overt and subclinical hyperthyroidism, are associated with the high risk of AF; so we adjusted hyperthyroidism in the multivariable model. We further estimated the relationship between AF and morphine used according to various age groups and CCI score levels. We also assessed the association between AF development and the duration of morphine use in the study period. All analyses were performed using the statistical package SAS Version 9.4 (SAS Institute Inc, Cary, NC), and the significance level was set at a *P* value of <0.05.

# RESULTS

Of the 73,917 patients in this study, 18,671 (25.3%) received morphine treatment, and 55,246 (74.7%) did not receive morphine treatment. The mean ages were 52.3, 52.6, and 52.2 years in all patients, morphine users, and nonmorphine users, respectively (standard deviation = 11.9, 12.2, and 11.8, Table 1). Compared with nonmorphine users, morphine users exhibited a higher CCI score (1.56% vs. 1.18% at CCI score 3+), and more of them received bisphosphonates (11.4% vs. 2.66%) and paclitaxel (10.7% vs. 5.30%). However, morphine users were less likely to receive tamoxifen (56.8% vs. 64.8%).

During the study period, morphine users exhibited 5.04- and 4.37-fold AF risks according to the crude and adjusted time-dependent Cox proportional hazard model compared with nonmorphine users (95% confidence interval [CI] = 4.13–6.15 and 3.56–5.36, Table 2). Compared with patients aged <50 years, the AF risk increased from 4.06 for patients aged 50 to 64 years to 21.7 for patients aged ≥65 years (95% CI = 3.07–5.36 and 16.7–28.2). An increase of 1 year in patient age was associated with a 10% AF risk increase (95% CI = 1.10–1.11). The AF risk also increased by 26% with a 1-point CCI score
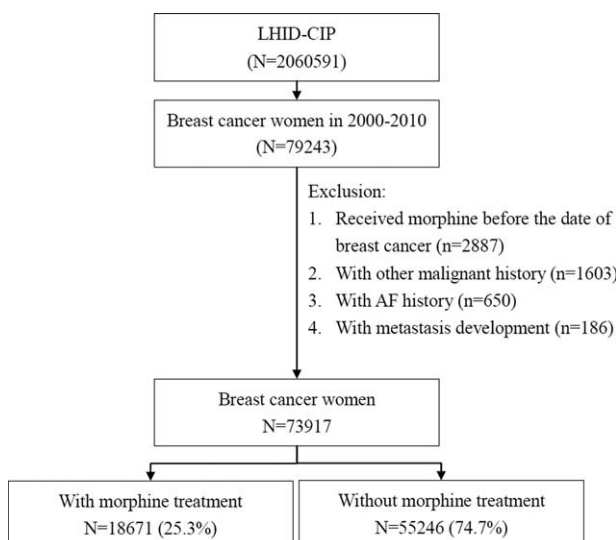
**TABLE 1.** Demographic of Age and Charlson's Comorbidity Index Score Between Patients With and Without Morphine Treatment

| | All N = 73,917 | | Morphine N = 18,671 | | Comparison N = 55,246 | | |
|---|---|---|---|---|---|---|---|
| | **n** | **%** | **n** | **%** | **n** | **%** | **P Value** |
| Age, yr | | | | | | | <0.0001 |
|   <50 | 35,147 | 47.6 | 8477 | 45.4 | 26,670 | 48.3 | |
|   50−64 | 27,515 | 37.2 | 7161 | 38.4 | 20,354 | 36.8 | |
|   65+ | 11,255 | 15.2 | 3033 | 16.2 | 8222 | 14.9 | |
| Mean (SD) | 52.3 | (11.9) | 52.6 | (12.2) | 52.2 | (11.8) | <0.0001 |
| Charlson comorbidity index score | | | | | | | <0.0001 |
|   0 | 67,953 | 91.9 | 16,848 | 90.2 | 51,105 | 92.5 | |
|   1−2 | 5021 | 6.79 | 1532 | 8.21 | 3489 | 6.32 | |
|   3+ | 943 | 1.28 | 291 | 1.56 | 652 | 1.18 | |
| Comorbidity | | | | | | | |
|   Hypertension | 915 | 1.24 | 246 | 1.32 | 669 | 1.21 | 0.25 |
|   Valvular heart disease | 73 | 0.10 | 15 | 0.08 | 58 | 0.10 | 0.35 |
|   Hyperlipidemia | 678 | 0.92 | 155 | 0.83 | 523 | 0.95 | 0.15 |
|   Hypothyroidism | 937 | 1.27 | 228 | 1.2 | 709 | 1.28 | 0.51 |
|   Hyperthyroidism | 2725 | 3.69 | 656 | 3.51 | 2069 | 3.75 | 0.15 |
| Bisphosphonates | 3597 | 4.87 | 2126 | 11.4 | 1471 | 2.66 | <0.0001 |
| Paclitaxel | 4930 | 6.67 | 2001 | 10.7 | 2929 | 5.30 | <0.0001 |
| Tamoxifen | 46,431 | 62.8 | 10,610 | 56.8 | 35,821 | 64.8 | <0.0001 |

$\chi^2$ : AF = atrial fibrillation, SD = standard deviation.

increase (95% CI = 1.18–1.35). Hyperthyroidism patients had a 1.67-fold AF risk than nonhyperthyroidism patients (95% CI = 1.13–2.45). It was worth paying attention, tamoxifen users had a lower AF risk than nonusers (HR = 0.81, 95% CI = 0.68–0.97).

Table 3 presents the association between AF risk and morphine use stratified according to age and CCI score using adjusted time-dependent Cox proportional hazard model. In age-specific risk analysis, morphine users aged <50 years exhibited the highest risk (HR = 4.68, 95% CI = 2.36–9.29), followed by ≥65 years (HR = 4.59, 95% CI = 3.56–5.91) and 50 to 64 years (HR = 3.51, 95% CI = 2.32–5.31) compared with nonmorphine users. For CCI score-specific risk analyses, the risk decreased with increasing CCI score, from 4.60 at ''0'' score (95% CI = 3.62–5.84), 4.39 at ''1 to 2'' score (95% CI = 2.79–6.90) to 2.50 at ''≥3'' score (95% CI = 1.09–5.73).

Table 4 shows the association between AF development and the duration of morphine use in the study period. Compared with nonusers, AF risk increased as the duration of morphine use increased, from 2.38 for 1 to 15 days, 3.61 for 16 to 30 days, to 4.20 for >30 days (95% CI = 1.98–2.87, 1.98–6.60, and 2.75–6.44, respectively).

## DISCUSSION

Our results evidenced an association between morphine treatment and an increased risk of AF in female patients with breast cancer. The risk of AF increased as the CCI score increased, decreased by tamoxifen treatment,[20] but was not linked to bisphosphonates and paclitaxel use.[21]

AF is prevalent in patients with either life-threatening or non-life-threatening cancer.[22–25] For female breast cancer patients in Taiwan, the mortalities were 35.1% and 16.2% in patients with and without AF, respectively. Our study

demonstrated that morphine treatment is associated with the risk of AF in patients with breast cancer; thus, morphine treatment may partly contribute to the increased overall AF occurrence in patients with cancer. Morphine binds to opioid receptors, whereas the δ- and κ-receptor subtypes are abundant in the human heart and contribute to age- and stress-related alterations of cardiac functions. Opioid receptors mediate cardioprotection by increasing intracellular calcium levels, opening mitochondrial $K_{ATP}$ channels, and activating protein kinase C. The expression of the opioid receptors is downregulated in AF patients, suggesting a loss of protective capacity in the fibrillating atrial tissue.[26] We hypothesize that morphine treatment reduces the number of opioid receptors, a process correlated with desensitization and tolerance to morphine,[27] in the atrial tissue, and thereby increases the risk of AF in cancer patients.

Our study showed that the incidence of AF is reduced by tamoxifen treatment. This result is similar to a previous study using a large Swedish randomized trial of adjuvant tamoxifen in women with early breast cancer, which demonstrated a reduced risk of AF in the 5-year treatment group.[20] Tamoxifen is associated with a reduced risk of coronary heart disease[28] and reduced mortality of coronary heart disease.[29] The putative mechanisms contributing to this protective effect can be classified into: effects on lipid metabolism, antioxidant effects, hormonal effects, and anti-inflammatory effects.[30,31] The lack of clear understanding of the biological mechanisms underlying the cardioprotective effect of tamoxifen warrants further studies.

Although our study used population-based NHIRD records rather than self-reported data on drug use, there are still several limitations. First, diagnoses in the TNHI claims records are primarily for administrative billing purposes and may not contain the examination details. We do not have the data of

**TABLE 2.** Hazard Ratio and 95% CI for AF Occurred and AF-Associated Risk Factor in Cox Proportional Hazard Regression With Time-Dependent Covariates

| | HR (95% CI) | |
| --- | --- | --- |
| | **Crude** | **Adjusted** |
| Morphine | | |
| No | 1.00 (reference) | 1.00 (reference) |
| Yes | 5.04 (4.13–6.15)[***] | 4.37 (3.56–5.36)[***] |
| Age, yr | | |
| <50 | 1.00 (reference) | 1.00 (reference) |
| 50–64 | 4.31 (3.27–5.70)[***] | 4.06 (3.07–5.36)[***] |
| 65+ | 25.4 (19.6–32.9)[***] | 21.7 (16.7–28.2)[***] |
| Per 1-yr increased | 1.11 (1.10–1.11)[***] | 1.10 (1.10–1.11)[***] |
| Comorbidity | | |
| Hypertension | | |
| No | 1.00 (reference) | 1.00 (reference) |
| Yes | 2.53 (1.60–3.99)[***] | 1.12 (0.64–1.97) |
| Valvular heart disease | | |
| No | 1.00 (reference) | – |
| Yes | 1.68 (0.24–12.0) | – |
| Hyperlipidemia | | |
| No | 1.00 (reference) | 1.00 (reference) |
| Yes | 1.89 (1.04–2.42)* | 0.93 (0.45–1.93) |
| Hypothyroidism | | |
| No | 1.00 (reference) | – |
| Yes | 1.27 (0.66–2.45) | – |
| Hyperthyroidism | | |
| No | 1.00 (reference) | 1.00 (reference) |
| Yes | 1.26 (0.86–1.86) | 1.67 (1.13–2.45)[**] |
| Charlson comorbidity index score | | |
| 0 | 1.00 (reference) | 1.00 (reference) |
| 1–2 | 3.89 (3.18–4.75)[***] | 1.50 (1.22–1.85)[***] |
| ≥3 | 9.38 (6.84–12.9)[***] | 2.33 (1.69–3.22)[***] |
| Per 1-score increased | 1.72 (1.63–1.81)[***] | 1.26 (1.18–1.35)[***] |
| Bisphosphonates | | |
| No | 1.00 (reference) | 1.00 (reference) |
| Yes | 1.76 (1.35–2.29)[***] | 0.90 (0.69–1.19) |
| Paclitaxel | | |
| No | 1.00 (reference) | – |
| Yes | 1.36 (0.92–2.02) | – |
| Tamoxifen | | |
| No | 1.00 (reference) | 1.00 (reference) |
| Yes | 0.63 (0.53–0.75)[***] | 0.81 (0.68–0.97)* |

Adjusted for morphine user, age, hypertension, hyperlipidemia, hyperthyroidism, Charlson comorbidity index score, bisphosphonates use, and tamoxifen use.

AF = atrial fibrillation, CI = confidence interval, HR = hazard ratio.
[*] $P < 0.05$.
[**] $P < 0.01$.
[***] $P < 0.001$.

**TABLE 3.** Hazard Ratio and 95% CI for AF Occurred in Morphine Users Compared With Nonusers Using Cox Proportional Hazard Regression With Time-Dependent Covariates Stratified by Age and Charlson's Comorbidity Index Score

| | Morphine Users Vs Nonusers HR (95% CI) |
| --- | --- |
| Age, yr | |
| <50 | 4.68 (2.36–9.29)[***] |
| 50–64 | 3.51 (2.32–5.31)[***] |
| 65+ | 4.59 (3.56–5.91)[***] |
| Charlson comorbidity index score | |
| 0 | 4.60 (3.62–5.84)[***] |
| 1–2 | 4.39 (2.79–6.90)[***] |
| ≥ 3 | 2.50 (1.09–5.73)[*] |

Manually adjusted for age, hypertension, hyperlipidemia, hyperthyroidism, Charlson comorbidity index score, bisphosphonates use, and tamoxifen use.

AF = atrial fibrillation, CI = confidence interval, HR = hazard ratio.
[*] $P < 0.05$.
[***] $P < 0.001$.

duration with inactivity or malnutrition, because the NHIRD does not provide lifestyle records. Moreover, NHIRD is deficient of detailed information on smoking, alcohol consumption, body mass index (BMI), socioeconomic status, and family history of systemic diseases. These are all probable risk factors for AF development, and might be indirectly associated with morphine use. Since BMI is a good predictor of hypertension, hyperlipidemia, and diabetes,[31] we adjusted the effects of hypertension, DM, and hyperlipidemia as a replacement to eliminate the confounding influence of BMI. Fourth, because cancer pain might influence mobility and muscle strength, we used a malignancy cohort to eliminate cancer-related confounding factors. However, a retrospective cohort study is subject to biases originated from adjustments made for confounding variables. Thus, in spite of meticulous design to control confounding factors satisfactorily, a bias attributable to unknown confounders may persist.

**TABLE 4.** Hazard Ratio and 95% CI for AF Occurred in Different Morphine Used Days Compared With Nonusers Using Cox Proportional Hazard Regression With Time-Dependent Covariates

| | HR (95% CI) | |
| --- | --- | --- |
| | **Crude** | **Adjusted** |
| None users | 1.00 (reference) | 1.00 (reference) |
| Morphine user, days | | |
| 1–15 | 2.52 (1.09–3.02)[***] | 2.38 (1.98–2.87)[***] |
| 16–30 | 3.75 (2.06–6.81)[***] | 3.61 (1.98–6.60)[***] |
| >30 | 4.38 (2.91–6.60)[***] | 4.20 (2.75–6.44)[***] |
| *P* for trend | <0.0001 | <0.0001 |

Manually adjusted for age, hypertension, hyperlipidemia, hyperthyroidism, Charlson comorbidity index score and bisphosphonates use and tamoxifen use.

AF = atrial fibrillation, CI = confidence interval, HR = hazard ratio.
[***] $P < 0.001$.

left ventricular ejection fraction (EF) for each patient due to a lack of individual data from cardio-ultrasonography; thus we could not identify AF occurring in low EF. Second, as all records listed in the NHIRD are anonymous, we were not able to get in touch with patients directly to investigate their morphine use. We were also unable to count morphine prescribed before 1996, which may lead to an underestimation of cumulative dosages and subsequently weaken the observed association. Third, we could not correlate the increased morphine

Our results indicate that AF incidence is associated with morphine treatment. Additional large-scale randomized clinical trials are required to confirm these findings before any definitive conclusions can be drawn. Patients with breast cancer currently under morphine administration should be monitored for AF to prevent stroke and all-cause death.

## REFERENCES

1. Jalife J, Kaur K. Atrial remodeling, fibrosis, and atrial fibrillation. *Trends Cardiovasc Med.* 2015;25:475–484.

2. Chen CH, Chen MC, Gibbs H, et al. Antithrombotic treatment for stroke prevention in atrial fibrillation: The Asian agenda. *Int J Cardiol.* 2015;191:244–253.

3. Schnabel RB, Yin X, Gona P, et al. 50 year trends in atrial fibrillation prevalence, incidence, risk factors, and mortality in the Framingham Heart Study: a cohort study. *The Lancet.* 2015;386:154–162.

4. Wang CC, Lin CL, Wang GJ, et al. Atrial fibrillation associated with increased risk of venous thromboembolism. A population-based cohort study. *Thromb Haemost.* 2015;113:185–192.

5. Hui DS, Morley JE, Mikolajczak PC, et al. Atrial fibrillation: a major risk factor for cognitive decline. *Am Heart J.* 2015;169: 448–456.

6. Majeed A, Moser K, Carroll K. Trends in the prevalence and management of atrial fibrillation in general practice in England and Wales 1994–1998: analysis of data from the general practice research database. *Heart.* 2001;86:284–288.

7. Feinberg WM, Blackshear JL, Laupacis A, et al. Prevalence, age distribution, and gender of patients with atrial fibrillation: analysis and implications. *Arch Intern Med.* 1995;155:469–473.

8. Zoni-Berisso M, Lercari F, Carazza T, et al. Epidemiology of atrial fibrillation: European perspective. *Clin Epidemiol.* 2014;6:213–220.

9. Chien KL, Su TC, Hsu HC, et al. Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. *Int J Cardiol.* 2010;139:173–180.

10. Portenoy RK, Lesage P. Management of cancer pain. *Lancet.* 1999;353:1695–1700.

11. Wiffen PJ, Wee B, Moore RA. Oral morphine for cancer pain. *Cochrane Database Syst Rev.* 2013;7:CD003868.

12. Stein EA. Morphine effects on the cardiovascular system of awake, freely behaving rats. *Arch Int Pharmacodyn Ther.* 1976;223:54–63.

13. Glauser FL, Downie RL, Smith WR. Electrocardiographic abnormalities in acute heroin overdosage. *Bull Narc.* 1977;29:85–89.

14. Labi M. Paroxysmal atrial fibrillation in heroin intoxication. *Ann Intern Med.* 1969;71:951–959.

15. Qureshi WT, O'Neal WT, Khodneva Y, et al. Association between opioid use and atrial fibrillation: the reasons for geographic and racial differences in stroke (REGARDS) study. *JAMA Intern Med.* 2015;175:1058–1060.

16. Chiang CE, Wang KL, Lip GY. Stroke prevention in atrial fibrillation: an Asian perspective. *Thromb Haemost.* 2014;111: 789–797.

17. Lee CW, Muo CH, Liang JA, et al. Association of intensive morphine treatment and increased stroke incidence in prostate cancer patients: a population-based nested case-control study. *Jpn J Clin Oncol.* 2013;43:776–781.

18. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. *J Clin Epidemiol.* 1993;46:1075–1079.

19. Charlson ME, Pompei P, Ales KL, et al. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis.* 1987;40:373–383.

20. Rosell J, Nordenskjold B, Bengtsson NO, et al. Effects of adjuvant tamoxifen therapy on cardiac disease: results from a randomized trial with long-term follow-up. *Breast Cancer Res Treat.* 2013;138: 467–473.

21. Kaakeh Y, Overholser BR, Lopshire JC, et al. Drug-induced atrial fibrillation. *Drugs.* 2012;72:1617–1630.

22. O'Neal WT, Lakoski SG, Qureshi W, et al. Relation between cancer and atrial fibrillation (from the REasons for Geographic And Racial Differences in Stroke Study). *Am J Cardiol.* 2015;115:1090–1094.

23. Guzzetti S, Costantino G, Vernocchi A, et al. First diagnosis of colorectal or breast cancer and prevalence of atrial fibrillation. *Intern Emerg Med.* 2008;3:227–231.

24. Imperatori A, Mariscalco G, Riganti G, et al. Atrial fibrillation after pulmonary lobectomy for lung cancer affects long-term survival in a prospective single-center study. *J Cardiothorac Surg.* 2012;7:4.

25. Erichsen R, Christiansen C, Mehnert F, et al. Colorectal cancer and risk of atrial fibrillation and flutter: a population-based case–control study. *Intern Emerg Med.* 2012;7:431–438.

26. Lendeckel U, Muller C, Rocken C, et al. Expression of opioid receptor subtypes and their ligands in fibrillating human atria. *Pacing Clin Electrophysiol.* 2005;28(suppl 1):S275–S279.

27. Al-Hasani R, Bruchas MR. Molecular mechanisms of opioid receptor-dependent signaling and behavior. *Anesthesiology.* 2011;115:1363–1381.

28. Braithwaite RS, Chlebowski RT, Lau J, et al. Meta-analysis of vascular and neoplastic events associated with tamoxifen. *J Gen Intern Med.* 2003;18:937–947.

29. Nordenskjold B, Rosell J, Rutqvist LE, et al. Coronary heart disease mortality after 5 years of adjuvant tamoxifen therapy: results from a randomized trial. *J Natl Cancer Inst.* 2005;97:1609–1610.

30. Grainger DJ, Schofield PM. Tamoxifen for the prevention of myocardial infarction in humans: preclinical and early clinical evidence. *Circulation.* 2005;112:3018–3024.

31. Ricci C, Gaeta M, Rausa E, et al. Long-term effects of bariatric surgery on type II diabetes, hypertension and hyperlipidemia: a meta-analysis and meta-regression study with 5-year follow-up. *Obes Surg.* 2015;25:397–405.