Antidepressants and Valvular Heart Disease
A Nested Case-Control Study in Taiwan
Chi-Hui Lin, MS, Fei-Yuan Hsiao, PhD, Yen-Bin Liu, MD, Susan Shur-Fen Gau, MD, PhD, Chi-Chuan Wang, PhD, and Li-Jiuan Shen, PhD

Abstract: Empirical evidence regarding the association between antidepressants and valvular heart disease (VHD) is scarce. Using Taiwan’s National Health Insurance Research database, this nested case-control study assessed the association between antidepressants and VHD in a Chinese population. Among a cohort of patients who used at least 3 prescription antidepressants, 874 cases with VHD and 3496 matched controls (1:4 ratio) were identified. Conditional logistic regression models were used to examine the timing, duration, dose and type of antidepressants use, and the risk of VHD. Current use of antidepressants was associated with a 1.4-fold increase in the risk of VHD (adjusted odds ratio [aOR] 1.44; 95% confidence interval [CI] 1.17–1.77). Among current users, a dose–response association was observed in terms of the cumulative duration and the cumulative antidepressant dose. Significantly higher risks of VHD were observed among the current users of tricyclic antidepressants (aOR 1.40 [1.05–1.87]). We found that the use of antidepressants was associated with a greater risk of VHD and that the risks varied according to different antidepressants.

(Medicine 95(14):e3172)

Abbreviations: AOR = adjusted odds ratio, CI = confidence interval, DDD = defined daily dose, ICD-9-CM = International Classification of Disease-Ninth edition-Clinical Modification, LHID = Longitudinal Health Insurance Database, NHI = National Health Insurance, NHIRD = National Health Insurance Research Database, SNRIs = serotonin-norepinephrine reuptake inhibitors, SSRIs = selective serotonin reuptake inhibitors, TCAs = tricyclic antidepressants, VHD = valvular heart disease.

KEY POINTS
• This study is the first to explore the association between the use of antidepressants and the risk of incident valvular heart disease (VHD) among an ethnic Chinese population.
• Current use of antidepressants was associated with a 1.4-fold increase in the risk of VHD.
• A dose–response association was observed in terms of the cumulative duration and the dose of antidepressants and the risk of VHD.

INTRODUCTION
Drug-induced valvular heart disease (VHD) primarily presents as cardiac-valvular regurgitation and has raised serious concerns as fenfluramine was withdrawn from the market.1–3 One of the possible mechanisms of drug-induced VHD is that some drugs may directly activate the 5-HT2B receptor located on the aortic and mitral valves, which would then lead to cardiac valve fibrosis.4–6 For example, drugs with well-known risks of causing VHD, such as appetite suppressants (e.g., fenfluramine), migraine prophylactics (e.g., ergotamine and methysergide), and antiparkinson agents (e.g., pergolide and cabergoline), have been reported to have high affinities and agonist activities at the 5-HT2B receptor.4–6

Nevertheless, several observational studies and animal studies have suggested other mechanisms of drug-induced VHD, such as elevations of 5-HT concentrations in the circulation and 5-HT transporter deficiencies.7–10 In patients with carcinoid syndrome tumors, high 5-HT levels have been observed to be associated with valvulopathy,11,12 and this association resembles the pattern of VHD developed in pergolide and cabergoline users.5,12 Animal studies have also reported that daily injections of 5-HT in rats result in both elevated 5-HT concentrations in the circulation and 5-HT transporter deficiencies.7–10

In the present study, we report that daily injections of 5-HT in rats result in both elevated 5-HT concentrations in the circulation and 5-HT transporter deficiencies.7–10

Supplemental Digital Content is available for this article.

https://www.md-journal.com/supplemental
develops in 5-HT transporter-knockout mice may result from a reduction of in the clearance of 5-HT and a subsequent elevation of the 5-HT level. Therefore, the development of drug-induced VHD probably results from a complex interaction between 5-HT, the 5-HT transporter, and the 5-HT<sub>2B</sub> receptor.

Together, these hypotheses illustrate the urgent need for more information about the safety of antidepressants. Although the pharmacologic mechanisms of antidepressants are related to serotonin metabolism, for example, inhibition of the 5-HT transporter and downregulation of the 5-HT transporter, empirical evidence regarding the safety of antidepressant treatments is scarce. Some studies have found that the use of antidepressants does not increase the risk of VHD. However, these studies are limited by small sample sizes, confounded by indications and suffer from unclearly defined populations. Therefore, this study aimed to evaluate the association between the use of antidepressants and VHD using a population-based large-scale cohort with 10 years of follow-up data.

MATERIAL AND METHODS

Data Sources
The National Health Insurance Research Database (NHIRD) is a claims-based database of Taiwan's mandatory National Health Insurance (NHI) program. The NHI program was launched in 1995 and covers >99% of Taiwan's population (~23 million residents). This database provides comprehensive records of healthcare utilization, including ambulatory care, inpatient care, and prescription medications, and has been used for pharmacoepidemiological research that has been published in many studies. Our study was based on a subset of the NHIRD, termed the Longitudinal Health Insurance Database (LHID), which contains the claim data of ~3 million individuals who were randomly sampled from the Registry for Beneficiaries of the NHIRD.

Ethical Statement
Because the identification numbers of all subjects in the NHIRD were encrypted to protect individual privacy, this study was exempted from full review by the Institution Review Board of the National Taiwan University Hospital, and the requirement for informed consent was waived. The Institution Review Board of the National Taiwan University Hospital approved this study (201312069W).

Study Cohort
We identified a cohort of patients aged 20 years and older who had received at least 3 prescriptions of antidepressants between January 1, 2002, and December 31, 2010. The date of the first antidepressants prescription was assigned as the cohort entry date. The patients who had used an antidepressant with 3 years prior the cohort entry date were excluded. Patients with diagnoses of VHD (International Classification of Disease-Ninth edition-Clinical Modification [ICD-9-CM] codes: 3961–9, 3970, 4240–3; who had undergone cardiac valve replacement (NHI codes: 68016A/B, 68017A/B, 68018A/B); had VHD-associated etiologies: rheumatic disease [ICD-9-CM codes: 391–5, 3971–9, 398], endocarditis [0932,421,4249], cardiomyopathy [425], carcinoid syndrome [2592], congenital heart disease [6485,746], pericarditis [420], myocarditis [422], or congestive heart failure [428], and those who had used drugs with potential risks of drug-induced VHD (ATC code for ergotamine N02CA02, N02CA52, N02CA72, A03CB31; pergolide N04BC02; cabergoline N04BC06, G02CB03; bro-mocriptine N04BC01, G02CB01) within 1 year before the cohort entry date were excluded.

Cases and Controls
Our cases and controls were selected from the identified cohort (i.e. patients aged 20 years and older who had received at least 3 prescriptions of antidepressants between January 1, 2002, and December 31, 2010). The cases were defined as patients who were first hospitalized with a diagnosis of VHD (ICD-9-CM codes 3961–9, 3970, 4240–3) or who were first hospitalized to receive a cardiac valve replacement (NHI code 68016A/B, 68017A/B, 68018A/B) between January 1, 2002, and December 31, 2010.). The admission date was defined as the index date. To further increase the validity of the identification of VHD cases, we required that all of the identified cases underwent echocardiography (NHI code 18005B, 18006B) 3 months before the index date. As the disease progression of VHD from the asymptomatic to the symptomatic stage typically requires 3 years or longer, only the cases who presented with VHD >3 years after the first use of antidepressants were retained to account for the latency period. Using incidence-density sampling, each case was matched with 4 controls according to age (±1 year), sex, and cohort entry date (±30 days).

Exposure Assessment
We retrieved all of the antidepressant prescriptions, including selective serotonin reuptake inhibitors (SSRIs; fluoxetine, paroxetine, sertraline, citalopram, escitalopram, and fluvoxamine), tricyclic antidepressants (TCAs; clomipramine, imipramine, maprotiline, amitriptyline, and dothiepin), serotonin-norepinephrine reuptake inhibitors (SNRIs; venlafaxine, duloxetine, and milnacipram), and other antidepressants (bupropion, mirtazapine, and trazodone, Appendix 1, http://links.lww.com/MD/A850), 3 years prior to the index dates of our study cohort. We created antidepressant exposure categories based on the timing and duration of the use of the identified prescriptions. Antidepressants users were categorized as current, recent, and past users based on the receipt of prescriptions for antidepressants within 180 days, between 181 and 365 days, and between 366 and 1095 days before the index date, respectively. Nonusers were defined as patients with no record of antidepressant use within 3 year before the index date.

We further examined the cumulative durations, cumulative doses and last daily doses of antidepressants to explore the dose-response relationship between the use of antidepressants and risk for VHD. The cumulative duration was calculated by summing all prescribed days of antidepressant use within the 3 years prior the index date. The cumulative dosage was computed according to the defined daily dose (DDD). The last daily dose was the daily dosage of the prescription nearest to the index date. If a patient received >1 antidepressant, we summed the daily doses of all of the antidepressants.

Exposure to antidepressants was categorized by the type of antidepressant, affinity for the 5-HT transporter and individual antidepressant. The antidepressants were classified into the following 3 categories according to their affinities for the 5-HT transporter: a high-affinity group (fluoxetine, paroxetine, sertraline, and clomipramine), a moderate-affinity group (citalopram, fluvoxamine, imipramine, venlafaxine, and amitriptyline), and a low-affinity group (trazodone, bupropion, mirtazapine, and dothiepin).
Statistical Analyses

We used McNemar’s test to compare the demographic characteristics between the cases and controls. Univariate conditional logistic regressions were used to estimate the crude association between each covariate and the risk of VHD. Multivariate conditional logistic regressions were used to evaluate the associations between the exposure to antidepressants and the risk of VHD. All of the multivariate models were adjusted for the comorbidities and co-medications of the patients based on the claims data for 1 year before the index date. The comorbidities included hypertension [ICD-9-CM codes: 401.xx-405.xx], diabetes [250.xx], lipid disorders [272.xx], chronic obstructive pulmonary disease [493.2, 496.xx], chronic kidney disease [585.xx], congestive heart failure [428.xx], myocardial infarction [410.xx-412.xx, 414.xx], cerebrovascular disease [430.xx-438.xx], and depression [296.x, 300.0, 300.4]. The co-medications included drugs with potential risks of causing VHD, including ergotamine, pergolide, cabergoline, and

FIGURE 1. Flowchart of the patient screening.
bromocriptine. The associations are presented as odds ratios (ORs) and 95% confidence intervals (CIs). The statistical test results were considered significant with a 2-sided $P$ value of $<0.05$. All data management and analyses were performed using SAS 9.3 for Windows (SAS Institute, Cary, NC).

**RESULTS**

Among 139,592 new users of antidepressants, we identified 874 cases of VHD and 3496 matched controls (Figure 1). The distributions of age, sex, and cohort entry date of the cases and controls were well matched. The cases were more likely to have co-morbid conditions than the controls. A greater proportion of cases were current users of antidepressants (28.5% vs 20.7%, Table 1).

After adjusting for the comorbidities, the current users of antidepressants were associated with a 1.4-fold increase in the risk of VHD (adjusted OR [aOR] 1.44; 95% CI [1.17–1.77]; $P<0.01$) compared with the nonusers. Neither the recent users (aOR 1.09; 95% CI [0.80–1.50]; $P=0.59$) nor the past users (aOR 1.01; 95% CI [0.81–1.25]; $P=0.94$) of antidepressants were associated with an increased risk of VHD compared with the nonusers. Additionally, we found that the patients with underlying congestive heart failure (aOR 4.04; 95% CI [3.14–5.19]), myocardial infarction (aOR 2.10; 95% CI [1.73–2.55]), chronic kidney disease (aOR 2.14; 95% CI [1.58–2.89]), hypertension (aOR 1.77; 95% CI [1.46–2.14]), and chronic obstructive pulmonary disease (aOR 1.62; 95% CI [1.23–2.14]) had higher risks of VHD (Table 2).

Among the current users of antidepressants, the aOR for VHD was the highest among those who used antidepressants for 91 to 180 days ($<90$ days, aOR 1.50; 95% CI [1.06–2.13]), 91 to 180 days (aOR 2.70 [1.68–4.32]), 181 to 365 days (aOR 1.10 [0.68–1.80]), and $>366$ days (aOR 1.30 [1.00–1.69]). The aOR of VHD increased with the cumulative dose of antidepressants (≤90 DDDs, aOR 1.54 [1.16–2.04]; 91–180 DDDs, aOR 1.58 [1.07–2.35]; and 181–365 DDDs, aOR 1.73 [1.14–2.63]). The risk of VHD did not differ from that of nonusers when the cumulative antidepressant dosage was $>366$ DDDs among the current users (Table 3).

The risks of VHD were significantly greater for current users who used TCAs (aOR 1.40; 95% CI [1.05–1.87]) and antidepressants with moderate (aOR 1.41; 95% CI [1.08–1.83]) or low (aOR 1.49; 95% CI [1.12–1.97]) affinities for the 5-HT transporter. The recent users of SNRIs (aOR 3.36; 95% CI [1.17–9.63]) were associated with an increased risk of VHD; however, the CIs varied widely (Table 4). The separate ORs for VHD were estimated for the exposures to individual antidepressants. We found that current users of citalopram (aOR 2.30; 95% CI [1.14–4.62]), duloxetine (aOR 4.77; 95% CI [1.89–12.02]), imipramine (aOR 1.40; 95% CI [1.03–1.91]), and trazodone (aOR 1.54; 95% CI [1.14–2.08]), and recent users of venlafaxine (aOR 4.09; 95% CI [1.89–12.02]) were associated with increased risks of VHD (Appendix 2, http://links.lww.com/MD/A850).

**DISCUSSION**

Via the application of a nested case-control study design to a nationwide-based cohort, this study is the first to explore the association between the use of antidepressants and the risk of incident VHD among an ethnic Chinese population. We found a 1.4-fold increase in the risk of VHD among current users of antidepressants. Among current users, a dose–response effect was found in patients with cumulative DDDs. Moreover, the users who were currently taking TCAs and antidepressants with moderate and low affinities for the 5-HT transporter were at significant higher risks of VHD.

**TABLE 1. Characteristics of the Cases and Matched Controls**

|                   | Case (N=874) n (%) | Control (N=3496) n (%) | $P$  |
|-------------------|--------------------|------------------------|------|
| Mean age (y ± SD) | 65.2 ±14.1         | 65.1 ±14.0             | <0.01* |
| Male (%)          | 398 (45.5)         | 1592 (45.5)            |      |
| Mean duration of follow-up (days ± SD) | 2007.3 ±620.7 | 2006.7 ±620.2 |      |

**Comorbidities**

- Hypertension: 604 (69.1) vs 1717 (49.1); $<0.01$*
- Diabetes: 296 (33.9) vs 836 (23.9); $<0.01$*
- Lipid disorder: 256 (29.3) vs 722 (20.7); $<0.01$*
- Chronic obstructive pulmonary disease: 112 (12.8) vs 217 (6.2); $<0.01$*
- Chronic kidney disease: 106 (12.1) vs 137 (3.9); $<0.01$*
- Congestive heart failure: 207 (23.7) vs 164 (4.7); $<0.01$*
- Myocardial infarction: 312 (35.7) vs 513 (14.7); $<0.01$*
- Cerebrovascular disease: 237 (27.1) vs 626 (17.9); $<0.01$*
- Depression: 41 (4.7) vs 121 (3.5); $<0.01$*

**Co-medications**

- Ergotamine: 40 (4.6) vs 138 (4.0); 0.19
- Pergolide: 3 (0.3) vs 6 (0.2); 0.16
- Bromocriptine: 5 (0.6) vs 18 (0.5); 0.74

**Timing of exposure to antidepressants**

- Non-user: 352 (40.3) vs 1698 (48.6); $<0.01$*
- Current user: 249 (28.5) vs 722 (20.7); $<0.01$*
- Recent user: 78 (8.9) vs 230 (6.6); $<0.01$*
- Past user: 195 (22.3) vs 846 (24.2); 0.06

* $P<0.05$.  

© 2016 Wolters Kluwer Health, Inc. All rights reserved.
TABLE 2. Crude and Adjusted Odds Ratios for the Risk of VHD and Exposure to Antidepressants

| Comorbidities in the past year                      | Crude OR (OR 95% CI) | P       | aOR§ (OR 95% CI) | P       |
|----------------------------------------------------|----------------------|---------|-----------------|---------|
| Hypertension                                       | 2.61 (2.20–3.10)     | <0.01*  | 1.77 (1.46–2.14) | <0.01*  |
| Diabetes                                           | 1.66 (1.41–1.95)     | <0.01*  | 1.09 (0.90–1.31) | 0.39    |
| Lipid disorder                                     | 1.63 (1.38–1.94)     | <0.01*  | 1.23 (1.01–1.49) | 0.04‡   |
| Chronic obstructive pulmonary disease              | 2.30 (1.79–2.85)     | <0.01*  | 1.62 (1.23–2.14) | <0.01*  |
| Chronic kidney disease                             | 2.88 (2.33–3.55)     | <0.01*  | 2.14 (1.58–2.89) | <0.01*  |
| Congestive heart failure                           | 6.56 (5.19–8.29)     | <0.01*  | 4.04 (3.14–5.19) | <0.01*  |
| Myocardial infarction                              | 3.36 (2.82–4.00)     | <0.01*  | 2.10 (1.73–2.55) | <0.01*  |
| Cerebrovascular disease                            | 1.76 (1.47–2.10)     | <0.01*  | 1.34 (1.10–1.64) | <0.01*  |
| Depression                                         | 1.37 (0.95–1.96)     | 0.09    | 1.15 (0.77–1.72) | 0.50    |

§ Adjusted for hypertension, diabetes, lipid disorder, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, myocardial infarction, cerebrovascular disease, and depression.

To our knowledge, empirical data regarding the association of the risk of VHD with antidepressants use are very limited. Our findings could thus add to the literature by exploring different definition of exposure to antidepressant and the risk for VHD. However, our findings are inconsistent with those from a matched case-control study conducted by Lapi et al.22 in which the authors reported that the risk of VHD was not associated with the use of antidepressants based on administrative claims data from the United Kingdom (aOR 1.16 [0.96–1.40] for current users compared with past users). Ours is the first study to show a positive association between the present use of antidepressants and the risk for VHD, and several factors may have contributed to the discrepancy between the findings of our study and that of Lapi et al.22 The major strength of our study is that we defined patients who were hospitalized with VHD as cases, whereas Lapi et al identified their cases based on inpatient and outpatient claims. Our approach thus identified more homogeneous cases because the severities of VHD identified in inpatient and outpatient settings could be very different. Additionally, we adopted a latency period of 3 years to exclude the cases with VHD that occurred too quickly for the antidepressant use to have contributed, which enhanced the

TABLE 3. Cumulative Duration, Cumulative Dose, and Last Daily Dose of Antidepressants and Risk of VHD Among Current Users

| Cumulative duration | Case (N = 874) n (%) | Control (N = 3496) n (%) | OR (95% CI) | P       | OR (95% CI) | P       |
|---------------------|----------------------|--------------------------|-------------|---------|-------------|---------|
| ≤90 days            | 61 (7.0)             | 170 (4.9)                | 1.75 (1.28–2.40) | <0.01*  | 1.50 (1.06–2.13) | 0.02‡   |
| 91–180 days         | 37 (4.2)             | 54 (1.5)                 | 3.29 (2.14–5.07) | <0.01*  | 2.70 (1.68–4.32) | <0.01*  |
| 181–365 days        | 26 (3.0)             | 96 (2.8)                 | 1.34 (0.86–2.09) | 0.20    | 1.10 (0.68–1.80) | 0.69    |
| ≥366 days           | 125 (14.3)           | 402 (11.5)               | 1.52 (1.20–1.92) | <0.01*  | 1.30 (1.00–1.69) | <0.05‡   |
| Cumulative dose     |                      |                          |             |         |             |         |
| ≤90 DDD             | 106 (12.1)           | 276 (7.9)                | 1.87 (1.45–2.42) | <0.01*  | 1.54 (1.16–2.04) | <0.01*  |
| 91–180 DDD          | 49 (5.6)             | 117 (3.4)                | 2.07 (1.44–2.95) | <0.01*  | 1.58 (1.07–2.35) | 0.02‡   |
| 181–365 DDD         | 40 (4.6)             | 106 (3.0)                | 1.81 (1.24–2.65) | 0.01†   | 1.73 (1.14–2.63) | 0.01†   |
| ≥366 DDD            | 54 (6.2)             | 223 (6.4)                | 1.18 (0.85–1.63) | 0.02‡   | 1.06 (0.75–1.51) | 0.74    |
| Last daily dose     |                      |                          |             |         |             |         |
| <1 DDD              | 164 (18.8)           | 459 (13.1)               | 1.74 (1.41–2.16) | <0.01*  | 1.46 (1.16–1.86) | <0.01*  |
| ≥1 DDD              | 85 (9.7)             | 263 (7.5)                | 1.59 (1.21–2.09) | <0.01*  | 1.39 (1.03–1.87) | 0.03‡   |

§ P < 0.01.
† P < 0.05.
‡ Adjusted with hypertension, diabetes, lipid disorder, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, myocardial infarction, cerebrovascular disease, and depression.
association between antidepressant exposure and subsequent VHD, whereas Lapi et al did not consider this issue. The criteria for the cohort selections in the 2 studies were also different. We chose patients who had at least 3 prescriptions of antidepressants, whereas Lapi et al examined those who had at least 1 prescription of antidepressants. Furthermore, Lapi et al stratified their analyses by the timing of the exposure to antidepressants and utilized patients with the smallest cumulative durations or the worst adherences as the reference group, which may have masked the effect of timing and the dose-response relationship. To address this limitation, we defined the reference group as those who had not used antidepressants within 3 years before the index date. Another possible explanation may be that our study cohort was composed of an ethnic Chinese population, which contrasts with the ethnicity of the population examined by Lapi et al.

Our findings regarding potential risk factors for VHD, such as congestive heart failure (aOR 2.7; \( P < 0.01 \)), coronary artery disease (aOR 1.4; \( P < 0.01 \)), and hypertension (aOR 1.6 [1.2–2.0]), were consistent with those of existing studies. We further found that patients with chronic kidney disease and chronic obstructive pulmonary disease were associated with greater risks of VHD. Thus, we suggest that patients who use antidepressants should pay more attention to the risk of VHD, especially those with underlying risk factors.

Our study also adds to the current evidence via the investigation of the risks of VHD associated with different types of antidepressants. Our negative findings regarding SSRI users and the risks of VHD are in line with those of 2 previous cohort studies. Using an inpatient sample with routine echocardiography in a medical centre as a study cohort, Mast et al demonstrated that the prevalence of regurgitation does not significantly differ between those who are receiving SSRIs and those who are not (26.7% vs 30.4%; \( P = 0.19 \)). Marechaux et al also showed that the risk of VHD in SSRI users is similar to that of non-SSRI users (7.7% vs 8.9%; \( P = 0.71 \)) among patients who have been exposed to benfluorex, which is an antidiabetic agent with a potential risk for causing VHD. However, by exploring the nationwide claims database, our study accessed a more general population than these 2 existing studies. As with all observational studies based on claim databases, some limitations related to this study should be recognized. First, the NIHIRD lacks physical parameters and social histories, including body mass indices and smoking histories, which may be associated with the risk of VHD. However, we used chronic obstructive pulmonary disease as a surrogate for smoking.

Table 4. Use of Antidepressants and Risk of VHD, Classified by Type of Antidepressants or Affinity for Serotonin Transporter

| Type of antidepressant | Case (N=874) n (%) | Control (N=3496) n (%) | Crude OR (95% CI) | aOR* (95% CI) |
|------------------------|-------------------|-----------------------|------------------|-------------|
| | | OR (95% CI) | \( P \) | OR (95% CI) | \( P \) |
| **SSRI** | | | | | |
| Current user | 75 (8.6) | 242 (6.9) | 1.52 (1.14–2.02) \( <0.01^* \) | 1.36 (0.99–1.86) | 0.06 |
| Recent user | 27 (3.1) | 92 (2.6) | 1.44 (0.92–2.25) | 0.11 | 1.18 (0.72–1.95) | 0.51 |
| Past user | 79 (9.0) | 298 (8.5) | 1.31 (1.00–1.73) | 0.05 | 1.19 (0.88–1.60) | 0.26 |
| **SNRI** | | | | | |
| Current user | 20 (2.3) | 60 (1.7) | 1.67 (0.99–2.82) | 0.06 | 1.67 (0.95–2.94) | 0.08 |
| Recent user | 6 (0.7) | 12 (0.3) | 2.56 (0.95–6.87) | 0.06 | 3.36 (1.17–9.63) | 0.02 |
| Past user | 20 (2.3) | 60 (1.7) | 1.67 (0.99–2.81) | 0.05 | 1.57 (0.88–2.78) | 0.12 |
| **TCA** | | | | | |
| Current user | 95 (10.9) | 261 (7.5) | 1.77 (1.36–2.30) | \( <0.01^* \) | 1.40 (1.05–1.87) | 0.02 |
| Recent user | 51 (5.8) | 131 (3.8) | 1.89 (1.34–2.67) | \( <0.01^* \) | 1.12 (0.76–1.65) | 0.57 |
| Past user | 138 (15.8) | 509 (14.6) | 1.33 (1.06–1.67) | 0.01 | 1.05 (0.82–1.35) | 0.71 |
| **Affinity for serotonin transporter** | | | | | |
| **HA group** | | | | | |
| Current user | 48 (5.5) | 178 (5.1) | 1.32 (0.94–1.85) | 0.11 | 1.15 (0.79–1.66) | 0.47 |
| Recent user | 22 (2.5) | 68 (2.0) | 1.59 (0.97–2.60) | 0.06 | 1.21 (0.70–2.10) | 0.49 |
| Past user | 68 (7.8) | 257 (7.4) | 1.31 (0.97–1.76) | 0.07 | 1.21 (0.88–1.66) | 0.24 |
| **MA group** | | | | | |
| Current user | 117 (13.4) | 328 (9.4) | 1.74 (1.37–2.22) | \( <0.01^* \) | 1.41 (1.08–1.83) | 0.01 |
| Recent user | 54 (6.2) | 149 (4.3) | 1.77 (1.26–2.47) | \( <0.01^* \) | 1.12 (0.77–1.62) | 0.56 |
| Past user | 153 (17.5) | 558 (16.0) | 1.35 (1.08–1.68) | \( <0.01^* \) | 1.09 (0.86–1.39) | 0.46 |
| **LA group** | | | | | |
| Current user | 104 (11.9) | 289 (8.3) | 1.76 (1.36–2.27) | \( <0.01^* \) | 1.49 (1.12–1.97) | \( <0.01^* \) |
| Recent user | 30 (3.4) | 86 (2.5) | 1.73 (1.11–2.67) | 0.01 | 1.29 (0.80–2.10) | 0.30 |
| Past user | 93 (10.6) | 364 (10.4) | 1.28 (0.98–1.65) | 0.07 | 1.16 (0.88–1.54) | 0.29 |

HA = high affinity, LA = low affinity, MA = moderate affinity.

* \( P < 0.01 \).

1 Users categorized by days between last prescription and index date: current user, \( \leq 180 \) days; recent user, 181–365 days; past user, 366–1095 days; ever user, \( >1095 \) days.

2 Adjusted with hypertension, diabetes, lipid disorder, chronic obstructive pulmonary disease, chronic kidney disease, congestive heart failure, myocardial infarction, cerebrovascular disease, and depression.

Copyright © 2016 Wolters Kluwer Health, Inc. All rights reserved.
history. Moreover, we adjusted for a broad variety of covariates in our model and still demonstrated a greater risk of VHD among the current users of antidepressants. Second, information about adherence to the prescribed medication regimens is not contained in the NHIRD. Finally, a larger sample size is required to investigate the relationships between different antidepressants and the risk of VHD as there were many categories with a small sample size (Appendix 2, http://links.lww.com/MD/A850).

CONCLUSIONS
This population-based study demonstrated that the current use of antidepressants was associated with an increased risk of VHD in a Chinese population in Taiwan. Furthermore, the risk varied between the different types of antidepressants, and this effect cannot be explained by the potencies of their pharmacodynamics or their pharmacokinetics properties. When patients with specific underline diseases use antidepressants, they should be closely monitored for the risk of VHD.

REFERENCES
1. Cosyns B, Droogmans S, Rosenhek R, et al. Drug-induced valvular heart disease. Heart. 2013;99:7–12.
2. Andrejak M, Tribouilloy C. Drug-induced valvular heart disease: an update. Arch Cardiovasc Dis. 2013;106:333–339.
3. Bhattacharyya S, Schapira AH, Mikhailidis DP, et al. Drug-induced fibrotic valvular heart disease. Lancet. 2009;374:577–585.
4. Roth BL. Drugs and valvular heart disease. N Engl J Med. 2007;356:6–9.
5. Smith SA, Waggoner AD, de las Fuentes L, et al. Role of serotoninergic pathways in drug-induced valvular heart disease and diagnostic features by echocardiography. J Am Soc Echocardiogr. 2009;22:883–889.
6. Rothman RB, Baumann MH, Savage JE, et al. Evidence for possible involvement of 5-HT2B receptors in the cardiac valvulopathy associated with fenfluramine and other serotonergic medications. Circulation. 2000;102:2836–2841.
7. Mekontso-Dessap A, Broui F, Pascal O, et al. Deficiency of the 5-hydroxytryptamine transporter gene leads to cardiac fibrosis and valvulopathy in mice. Circulation. 2006;113:81–89.
8. Elangbam CS, Job LE, Zadrozy NM, et al. 5-Hydroxytryptamine (5HT)-induced valvuopathy: compositional valvular alterations are associated with 5HT2B receptor and 5HT transporter transcript changes in Sprague–Dawley rats. Exp Toxicol Pathol. 2008;60:253–262.
9. Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation. 1995;92:790–795.
10. Gustafsson BITK, Nordrum I, Loennechen JP, et al. Long-term serotonon administration induces heart valve disease in rats. Circulation. 2005;111:1517–1522.
11. Connolly HMCJ, McGoon MD, Hensrud DD, et al. Valvular heart disease associated with fenfluramine-phenethamine. N Engl J Med. 1997;337:581–588.
12. Horvath JFR, Kleiner-Fisman G, Lerch R, et al. Severe multivalvul heart disease: a new complication of the ergot derivative dopamine agonists. Mov Disord. 2004;19:656–662.
13. Rothman RB, Redmon JB, Raatz SK, et al. Chronic treatment with phentermine combined with fenfluramine lowers plasma serotonin. Am J Cardiol. 2000;85:913–915.
14. Lee SLFB. Serotonin uptake by bovine pulmonary endothelial cells in culture, II: stimulation by hypoxia. Am J Physiol. 1986;250:C766–770.
15. Eddahibi SHM, Fadel E, Raffestin B, et al. Serotonin transporter overexpression is responsible for pulmonary artery smooth muscle hyperplasia in primary pulmonary hypertension. J Clin Invest. 2001;108:1141–1150.
16. Levy RJ. Serotonin transporter mechanisms and cardiac disease. Circulation. 2006;113:2–4.
17. Mann JJ. The medical management of depression. N Engl J Med. 2005;353:1819–1834.
18. Mirza NR, Nielsen EO, Troelsen KB. Serotonin transporter density and anxiolytic-like effects of antidepressants in mice. Prog Neuropsycho- pharmacol Biol Psychiatry. 2007;31:858–866.
19. Zhang S, Li B, Lovatt D, et al. 5-HT2B receptors are expressed on astrocytes from brain and in culture and are a chronic target for all five conventional ‘serotonin-specific reuptake inhibitors’. Neuron Glia Biol. 2010;6:113–125.
20. Diaz SL, Doly S, Narboux-Neme N, et al. 5-HT(2B) receptors are required for serotonin-selective antidepressant actions. Mol Psychiatry. 2012;17:154–163.
21. Mast ST, Gering KR, Anstrom KJ, et al. Association between selective serotonin-reuptake inhibitor therapy and heart valve regurgitation. Am J Cardiol. 2001;87:989–993.
22. Lapi F, Nicolota F, Scotti L, et al. Use of antidepressant serotoniner- gic medications and cardiac valvulopathy: a nested case-control study in the health improvement network (THIN) database. Br J Clin Pharmacol. 2012;74:536–544.
23. Marechaulx S, Jeu A, Jobic Y, et al. Impact of selective serotonin reuptake inhibitor therapy on heart valves in patients exposed to fenfluraminex: a multicentre study. Arch Cardiovasc Dis. 2013;106:349–356.
24. Tsang S, Li B, Lovatt D, et al. Kinetics of 5-HT(2A) receptors and agonists of 5-HT2A receptors in the cardiac valve. J Am Soc Echocardiogr. 2009;22:883–889.
25. Robiolio PA, Rigolin VH, Wilson JS, et al. Carcinoid heart disease. Correlation of high serotonin levels with valvular abnormalities detected by cardiac catheterization and echocardiography. Circulation. 1995;92:790–795.
26. Gustafsson BITK, Nordrum I, Loennechen JP, et al. Long-term serotonon administration induces heart valve disease in rats. Circulation. 2005;111:1517–1522.
27. Connolly HMCJ, McGoon MD, Hensrud DD, et al. Valvular heart disease associated with fenfluramine-phenethamine. N Engl J Med. 1997;337:581–588.
28. Horvath JFR, Kleiner-Fisman G, Lerch R, et al. Severe multivalvul heart disease: a new complication of the ergot derivative dopamine agonists. Mov Disord. 2004;19:656–662.
29. Rothman RB, Redmon JB, Raatz SK, et al. Chronic treatment with phentermine combined with fenfluramine lowers plasma serotonin. Am J Cardiol. 2000;85:913–915.