行政院國家科學委員會專題研究計畫 期末報告

台灣骨質疏鬆族群於醫療利用及用藥安全之性別差異

計 畫 類 別 ：個別型
計 畫 編 號 ：NSC 101-2629-B-006-001-
執 行 期 間 ：101 年 08 月 01 日至 102 年 10 月 31 日
執 行 單 位 ：國立成功大學臨床藥學與藥物科技研究所

計 畫 主 持 人：高雅慧

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報 告 附 件 ：出席國際會議研究心得報告及發表論文

公 開 資 訊 ：本計畫涉及專利或其他智慧財產權，2 年後可公開查詢

中 華 民 國 102 年 10 月 23 日

中 文 摘 要 ： 研究背景

骨質疏鬆症引起之骨鬆骨折及其後遺症對於老年族群來說是很嚴重的併發症，不但會影響生活品質，亦有可能會增加未來骨折再發甚至死亡的風險。臨床上有許多骨質疏鬆藥品(例如: 雙磷酸鹽類藥物、raloxifene 及 calcitonin)可降低已發生骨鬆骨折之病患再發的風險。不過，骨質疏鬆症於病理學、流行病學與治療情況上皆存在著性別差異。雖然女性發生骨鬆骨折之風險高於男性，但是男性於發生骨鬆骨折後之預後卻比女性為差。更重要的是，男性病患接受骨鬆藥物之治療率於歐美等先進國家是遠低於女性的。以上資訊主要來自國外，但相關資訊於台灣尚不足。此外，近年亦有報告指出骨鬆族群可能較一般大眾有較高發生靜脈栓塞之風險，原因可能來自疾病本身或骨鬆藥品之使用，但此一議題於歐美國家尚未有定論。因此，探討國人骨鬆族群發生骨鬆骨折之預後、接受治療情況是否有性別差異是必須的，同時建立發生靜脈栓塞之流行病學資料、與骨鬆藥品可能之相關性亦有必要。

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研究方法

於性別差異之探討，本研究採用回溯性世代研究法(retrospective cohort study)，由 2003 至 2006 年 20 歲以上新發生過骨鬆骨折的病患中，自第一次骨折開始追蹤，分析其接受治療的比例與醫療利用之情況。此外，亦分析骨鬆骨折病患非脊椎骨折再發與性別上之差異。於國人骨鬆族群發生靜脈栓塞與骨鬆藥品使用之相關性部分，本研究自開始使用骨質疏鬆藥品 (alendronate, raloxifene 或 calcitonin)的時間點，往後追蹤。而靜脈栓塞則為探討骨鬆藥品安全性時之主要研究目標。本研究利用多變項 Cox regression 控制相關之共變數、評估相對危險比及描繪校正後之存活曲線。本研究亦會利用傾向分數 (propensity score)，以及一系列之敏感度測試來確認研究之可信度。所有資料處理及統計皆使用 SAS 9.2 版統計軟體。

研究結果

本研究發現，新發生骨鬆骨折族群，於醫療利用情況與未

來骨折再發之風險上，存有性別差異。女性較男性易接收到骨鬆骨折之治療、時機點亦較早。不過，不論男性或女性，治療比例仍然偏低。此外，雖然女生骨鬆骨折再發之風險較男性為高，但是此現象在骨折發生後三年出現逆轉，暗示男性治療比例的偏低仍然會對未來骨鬆骨折發生有顯著地影響。另一方面，本研究發現骨鬆骨折族群中，發生靜脈栓塞的比例，女性較男性高。儘管如此，使用 alendronate 或 raloxifene，相較於 calcitonin，不會增加靜脈栓塞發生之風險。

中文關鍵詞： 骨質疏鬆症、性別差異、醫療資源利用、靜脈栓塞

英文摘要： Background
There was no clear evidence for the association between oral bisphosphonates or raloxifene and venous thromboembolism (VTE). There might also has ethnic differences in VTE risk.
Objective
To compare the incidence and risk of VTE of different classes of osteoporosis drugs in Taiwan osteoporotic fracture population.
Method
A retrospective cohort study from 2003~2007, up to 6 years follow-up. Enrollees in Taiwan National Health Insurance, patients over 50 years old, with vertebral/hip fracture and new to osteoporosis therapy were recruited. Patients were classified into alendronate, calcitonin or raloxifene group according to the exposure after follow-up. The primary outcome of our study was all incident VTE, including deep vein thrombosis and pulmonary embolism. Cox proportional hazard models were used to compare the relative VTE risk among alendronate, raloxifene and calcitonin groups under on-treatment scenario.
Results
Our study found that there were sex differences in the health resource utilization and fracture outcomes after their first osteoporotic fracture occurred. Female patients were more likely and timely to receive osteoporosis drug treatments, as compared with male patients. Nevertheless, both genders were still under-treatment after fracture occurred, only less than 50% of patients received pharmacological

treatments. The higher secondary fracture incidence of male patients 3 years after index date may also reflected the results of more under-treatment of male patients, as compared with female patients. There were 25,443, 9,642 and 31,900 patients in the alendronate, raloxifene and calcitonin groups, and the mean age was 74.5 years (SD, 9.6). The incidence of VTE in alendronate, raloxifene and calcitonin groups was 11.2, 8.5 and 18.8 per 10,000 person-years. Results from Cox analyses showed alendronate or raloxifene recipients did not have higher risk for VTE as compared to calcitonin recipients (adjusted HR for alendronate: 0.84； 95%CI, 0.47-1.51； adjusted HR for raloxifene: 0.64； 95%CI, 0.33-1.28).
Conclusion
This retrospective analysis found that the incidence of VTE in Taiwanese osteoporosis patients was low, and the risk of VTE was similar across alendronate, raloxifene and calcitonin recipients in patients with osteoporotic fractures who were new to osteoporosis therapy.

英文關鍵詞： osteoporosis, sex difference, health resource utilization, venous thromboembolism

行政院國家科學委員會補助專題研究計畫 ■ 成 果 報 告 □ 期中進度報告

台灣骨質疏鬆族群於醫療利用及用藥安全之性別差異

計畫類別：■ 個別型計畫　　□ 整合型計畫
計畫編號：101-2629-B-006-001-
執行期間： 101 年 08 月 01 日 至 102 年 10 月 31 日

計畫主持人：高 雅 慧
共同主持人：楊 俊 佑
計畫參與人員： 林子傑、張雅淳、廖欣儀

成果報告類型(依經費核定清單規定繳交)：□精簡報告 ■完整報告

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■出席國際學術會議心得報告及發表之論文各一份
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處理方式：除產學合作研究計畫、提升產業技術及人才培育研究計畫、列管計畫及下列情形者外，得立即公開查詢
□涉及專利或其他智慧財產權，□一年■二年後可公開查詢

執行單位：國立成功大學 臨床藥學研究所
中 華 民 國 102 年 10 月 31 日

中文摘要

研究背景

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比例仍然偏低。此外，雖然女生骨鬆骨折再發之風險較男性為高，但是此現象在骨折發生後三年出現逆轉，暗示男性治療比例的偏低仍然會對未來骨鬆骨折發生有顯著地影響。另一方面，本研究發現骨鬆骨折族群中，發生靜脈栓塞的比例，女性較男性高。儘管如此，使用 alendronate 或 raloxifene，相較於 calcitonin，不會增加靜脈栓塞發生之風險。

Abstract

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Index

The sex differences in health utilization of Taiwan osteoporotic fracture patients

Incidence and Risk of Venous Thromboembolism among Taiwan Osteoporotic Fracture Population under Osteoporosis Pharmacological Treatments

1 Introduction

Osteoporosis is a silent disease characterized by decreased bone mass, deterioration of bone tissue and disruption of bone architecture, compromised bone strength, and increased fracture risk (1). Moreover, osteoporosis patients may be more susceptible to venous thromboembolism (VTE) due to aging, and which is also prevalent with fractures, immobilization, hospitalization and surgery all of which are known risk factors for VTE (2-5). Results from a large British cohort also found osteoporotic women may have 75% higher VTE risk as compared with non-osteoporotic women (6).

Besides osteoporosis itself, the literature addresses adverse cardiovascular events associated with bisphosphonates and raloxifene, which are the mainstay of pharmacological therapy for osteoporosis in the United States and Europe (7, 8). Significantly higher rate of serious atrial fibrillation events have been found in once-yearly zolendronate recipients, as compared with placebo (9), but no clear associations were found in recent observational studies using health insurance database (10-13). Nevertheless, it was reported that use of bisphosphonates was associated with increased risk of superficial phlebitis (14, 15). As for raloxifene, results from a clinical trial found it was associated with increased risk of deep venous thromboembolism (DVT) and pulmonary embolism (PE) in postmenopausal women (16), and that has been further confirmed by a recent meta-analysis (17). However, no clinically significant adverse cardiovascular effects were reported for calcitonin (7). The association between the use of oral bisphosphonates or raloxifene and VTE has been examined in real-life settings. Results from Danish population-based studies showed that alendronate and raloxifene recipients had a higher risk for VTE as compared with the general population but the risk increased before the start of treatment, suggesting the association might be related to osteoporosis itself (18, 19). Additionally, a recent British study found alendronate recipients did not have higher

risk for VTE as compared with untreated osteoporotic women (6). Therefore, there was no obvious evidence for the association between oral bisphosphonates or raloxifene and VTE in Western countries. However, it is unclear whether the baseline VTE risk in different races or ethnicities might have impacted the relationships between osteoporotic treatments and VTE risk. Our previous work found the incidence of VTE among the general population of Taiwan was only one-seventh of that among Caucasians (20). Whether the risk of VTE among the Taiwanese osteoporosis population undergoing alendronate or raloxifene treatment differs from other osteoporosis drug is an important issue warrants further investigation. Since year 2002, the reimbursement scheme in Taiwan's Bureau of National Health Insurance (BNHI) has restricted the use of osteoporosis drugs (alendronate, raloxifene, calcitonin nasal spray) to patients who have already experienced osteoporotic vertebral or hip fracture, thus enabling us to assess the incidence and risk of VTE in the Taiwanese osteoporotic fracture population, who are known to have more risk factors of VTE. Our study objectives were to compare the incidence and risk of VTE of different classes of osteoporosis drugs. Calcitonin, which is not known to be associated with VTE, was selected as the control group.

2 Method, health sources utilization

Data source

Datasets were obtained from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan launched a single-payer National Health Insurance (NHI) program in 1995, and by 2007, 99% of the population was enrolled. The NHIRD comprises demographic data of enrollees, information on healthcare professionals and medical facilities, and service records and expenditure claims from inpatient, ambulatory care, and contracted pharmacies for reimbursement purposes. Large computerized databases are provided to scientists in Taiwan for research purposes. The study

protocol of this study was reviewed and approved by the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan.

3 Study design and population, health sources utilization

This study is a retrospective cohort analysis that included treatment naïve patients aged above 50 years with new osteoporotic vertebral or hip fracture (ICD 9th CM code 733.13, 733.14, 805, 820) between 2003 and 2008. The index date was defined as the 1st date on which patients' fracture occurred. The baseline period was defined as the one year before the index date. Patients were excluded if they had any prior vertebral/hip fracture during the baseline period. Further, we excluded conditions that may be associated with osteoporosis severity: patients whose index osteoporotic fracture was associated with car accident or high impact trauma (ICD 9 code, E810-E819, E881-E883, E8841) or those with diagnosis of Paget's disease (ICD 9 code, 731.0) or malignant neoplasm (ICD 9 code, 140-208) during the baseline period. Finally, we excluded patients with past history of DVT (ICD 9 code, 4511, 4512, 4519, 4532, 4534, 4538, 4539, 45181) or PE (ICD 9 code, 4151).

Sex differences in health resource utilization

During the study period, drugs reimbursed for osteoporosis patients in Taiwan were alendronate, calcitonin, raloxifene and teriparatide. The proportion of osteoporotic fracture patients received osteoporosis drugs therapy, gap between fractures and treatment initiation, and classes of osteoporosis of drugs were assessed after the index fractures. Total supply in days and quantity of drugs were estimated from pharmacy claims originating from the inpatient and outpatient settings and contracted pharmacies of NHIRD.

Outcomes and Covariates

The primary outcome of our study was the risk of incident secondary non-vertebral fracture (hip, humerus or radius fractures), while the secondary outcome was the risk of hip fracture only; all outcomes were derived from inpatient claims. Patient demographic information was identified at treatment initiation and other covariates were determined by medical and pharmacy claims 1 year before the index date. The following covariates were included for assessing the study outcomes: demographic characteristics (age, gender), osteoporosis-related factors (osteoporosis, kyphosis), fracture history (non-vertebral fractures other than radius/ulna or hip fracture), and co-morbid conditions that might increase fracture risk (Alzheimer's disease, asthma, diabetes, ischemic stroke, history of falls, rheumatic arthritis).

Statistical analysis

Differences between female and male patients in patient demographic information and other covariates were determined either by student t-test or chi-square test. Further, the Kaplan-Meier method was used to present event rates and time-to-event curves in both genders.

4 Results, health sources utilization

Study population and baseline characteristics

From 2003-2008, there were 461,349 patients ever experienced vertebral/hip fractures. After we excluding patients aged below 50 years, patients with Paget's disease, cancer or whose fractures were associated with car accident, there were 316,556 patients included in our study cohort. Among them, 69.2% were female and 30.8% were male patients (Figure 1).

There were large differences in the baseline characteristics between female and male osteoporotic fracture patients. Female patients were older, more prevalent in osteoporotic vertebral fractures, osteoporosis diagnosis, cataracts, diabetes, and renal diseases, as compared with male patients. However, male patients were more prevalent in hip fractures, ischemic stroke, COPD, liver disease and Parkinsonism. Further, the socieoecnomic conditions were generally better in male patients. Finally, the crude secondary non-vertebral fracture rates were significantly higher in female patients (12.23% vs. 10.91%). Similar pattern could be found when we focused on hip fracture only (Table 1).

The sex differences in the health resource utilization

The pattern of health resource utilization was also imbalance between female and male patients after fracture occurred. 47.6% of female patients received osteoporosis drugs therapy, in contrast with only 20.29% of male patients received treatment. Further, female patients were received treatment earlier, and most of them received treatment with 30 days of fracture occurred. Finally, most prevalent pharmacological therapy for both genders was bisphosphonates and calcitonin

(61-65%; 46-49%, respectively). Due to the indication in Taiwan, 28% of female patients ever received raloxifene therapy as well (Table 2).

Kaplan-Meier analysis non-vertebral fracture incidence between Female and male

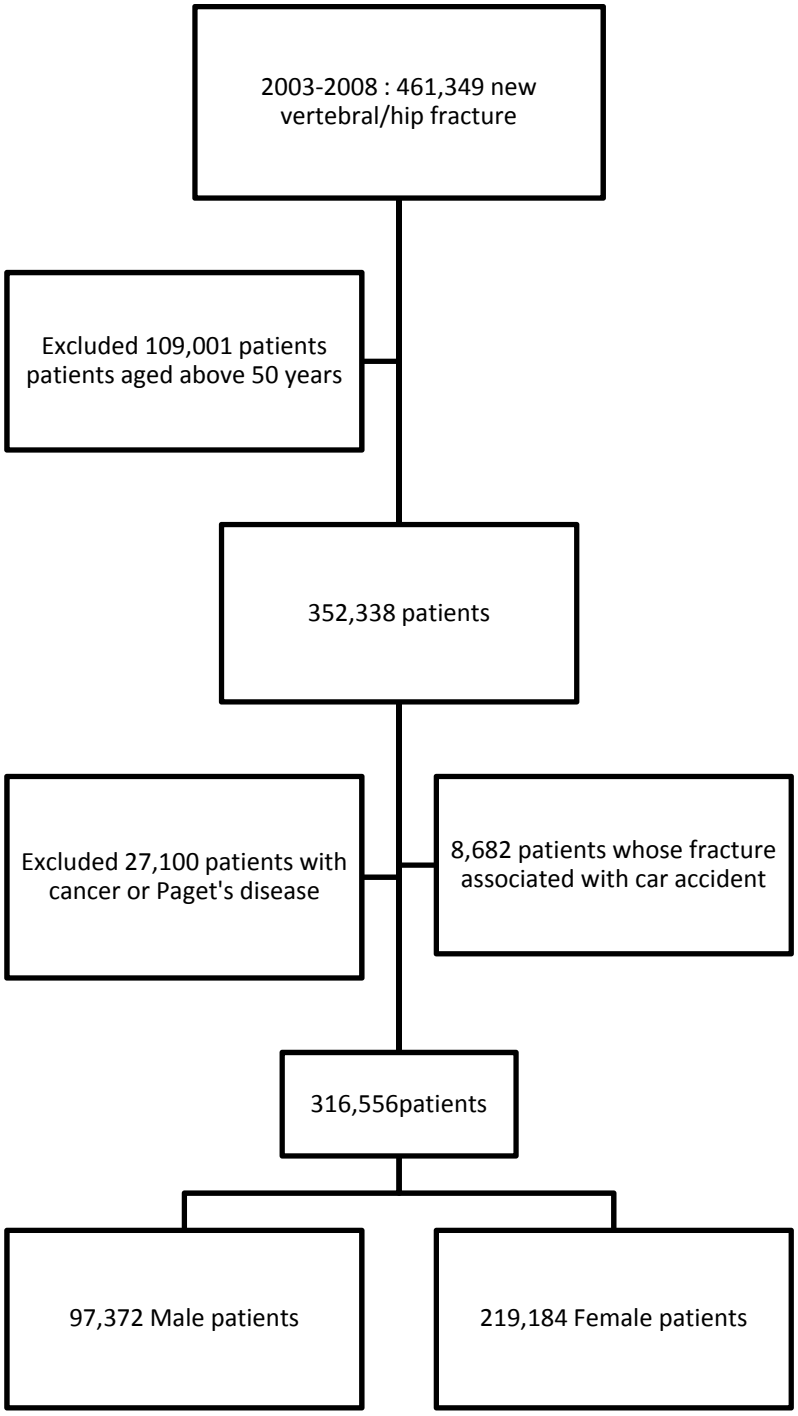
Figure 2 depicted the cumulative incidence of secondary non-vertebral fractures in both genders. Although the secondary non-vertebral fractures rates was higher in female patients in the first 3 years, however, there was a trend suggested that male patients suffered from higher secondary fracture incidence after 3 years of fracture occurred.

5 Discussion, health sources utilization

Our study found that there were sex differences in the health resource utilization and fracture outcomes after their first osteoporotic fracture occurred. Female patients were more likely and timely to receive osteoporosis drug treatments, as compared with male patients. Nevertheless, both genders were still under-treatment after fracture occurred, only less than 50% of patients received pharmacological treatments. The higher secondary fracture incidence of male patients 3 years after index date may also reflected the results of more under-treatment of male patients, as compared with female patients.

Based on our preliminary study results, the government and health care professionals in Taiwan should take action to promote the treatments for osteoporosis, especially in male patients, which is long ignorance problem.

Figure 1 Study inclusion flowchart



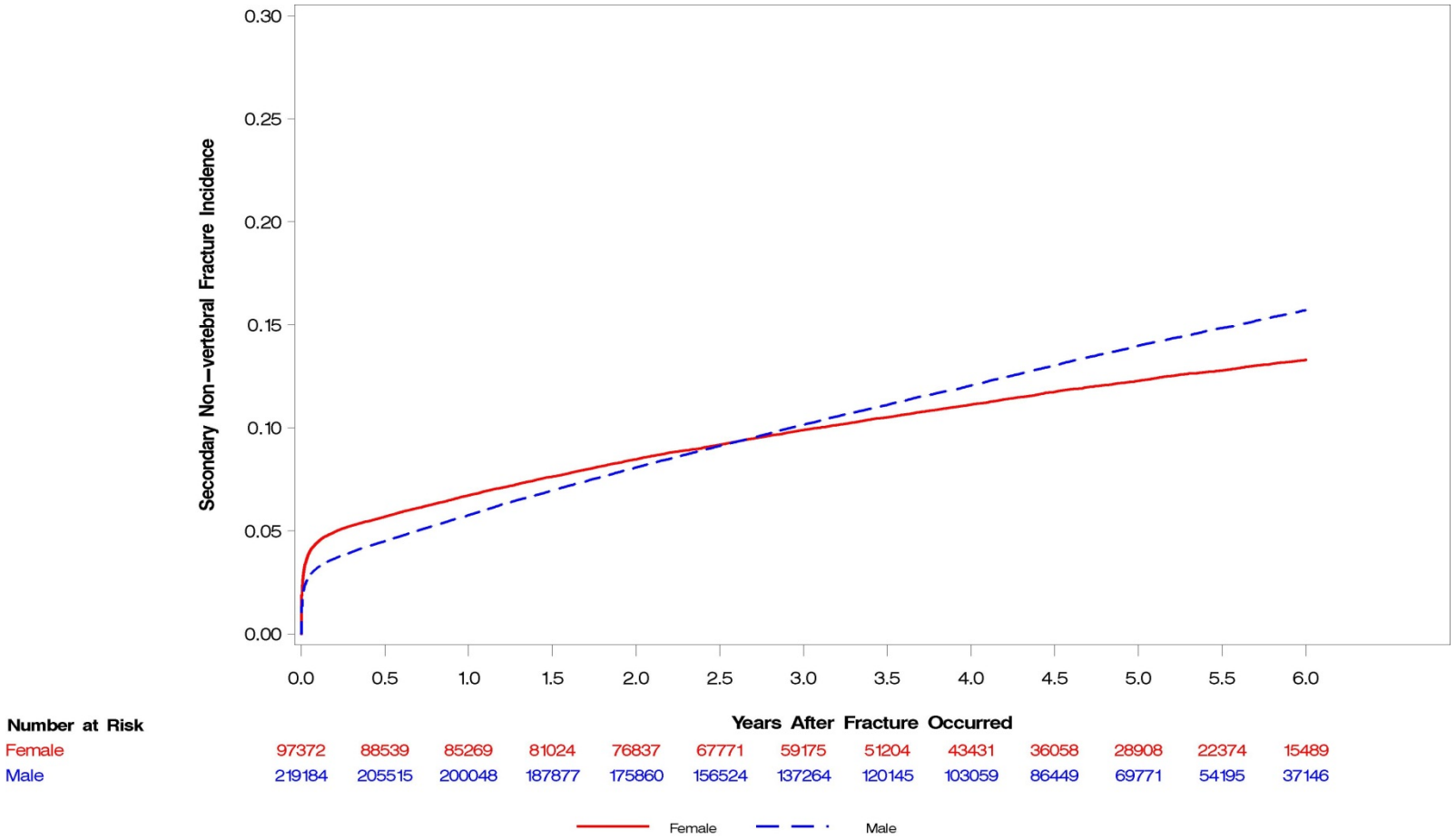


Figure 2 Kaplan-Meier analysis of secondary non-vertebral fracture incidence between Female and male

Table 1 Baseline characteristics of new osteoporosis drug users

	Female (219,184)	Male (N=97,372)	P value
Mean age, (SD), y	73.42 (10.36)	72.28 (11.24)	<0.0001
Index osteoporotic fracture			<0.0001
Hip, %	27.42	39.73	
Vertebral, %	72.58	60.27	
Comorbid conditions, %			
Osteoporosis	44.38	20.47	<0.0001
Kyphosis	1.88	1.23	<0.0001
Other non-vertebral fracture	14.14	16.78	<0.0001
Alzhelmer's disease	7.19	8.81	<0.0001
Asthma or COPD	20.18	30.49	<0.0001
Cataracts	22.72	18.28	<0.0001
Crohn's disease	16.20	14.01	<0.0001
Depression	6.58	5.26	<0.0001
DM	26.17	21.17	<0.0001
Fall	9.73	10.61	<0.0001
Hyperthyroidism	1.13	0.34	<0.0001
Ischemic stroke	8.84	12.13	<0.0001
Liver disease	9.79	10.55	<0.0001
Parkinsonism	5.08	6.09	<0.0001
Renal disease	4.14	3.88	0.0007

Table 1 Baseline characteristics of new osteoporosis drug users (Continued)

	Female (219,184)	**Male (N=97,372)**	**P value**
Rheumatoid arthritis	3.41	1.91	<0.0001
Occupation	55.95	72.42	<0.0001
Income			<0.0001
Low	44.04	27.57	
Middle	15.08	35.03	
High	40.88	37.40	
Crude secondary fracture rate,%			
Non-vertebral	12.23	10.91	<0.0001
Hip	8.17	5.67	<0.0001

* COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus

†Non-vertebral fractures: humerus, radius/ulna and hip fracture

Table 2 Health resource utilization

	Female (219,184)	**Male (N=97,372)**	**P value**
Received treatment,%	47.56	20.29	<0.0001
Treatment within 30 days	64.68	57.04	<0.0001
More than 180 days	22.06	26.22	<0.0001
Treatment gap since fracture (days)			<0.0001
Mean (SD)	196.5 (421.6)	238.5 (458.8)	
Median	12	19	
Pharmacological treatments,%	(N=104,244)	(N=19,759)	<0.0001
Bisphosphonates	61.55	65.30	
Raloxifene	28.11	1.35	
Calcitonin	46.48	49.39	
Teriparatide	4.62	3.48	

Incidence and Risk of Venous Thromboembolism among Taiwan Osteoporotic Fracture Population under Osteoporosis Pharmacological Treatments

1 Materials and Methods

Data source

Datasets were obtained from Taiwan's National Health Insurance Research Database (NHIRD). Taiwan launched a single-payer National Health Insurance (NHI) program in 1995, and by 2007, 99% of the population was enrolled. The NHIRD comprises demographic data of enrollees, information on healthcare professionals and medical facilities, and service records and expenditure claims from inpatient, ambulatory care, and contracted pharmacies for reimbursement purposes(21). Large computerized databases are provided to scientists in Taiwan for research purposes. The study protocol of this study was reviewed and approved by the Institutional Review Board of National Cheng Kung University Hospital, Tainan, Taiwan.

Study design and population

This study is a retrospective cohort analysis that included treatment naïve patients aged above 50 years with new osteoporotic vertebral or hip fracture (ICD 9th CM code 733.13, 733.14, 805, 820) and who were new to osteoporosis drug therapy between 2003 and 2007. Patients were considered as new users if they did not have any osteoporosis drug prescription (alendronate, raloxifene, calcitonin nasal spray) during the baseline period. The index date was defined as the 1st date on which patients received a treatment after the new osteoporotic fractures. The baseline period was defined as the one year before the index date. Patients were excluded if they had any

prior vertebral/hip fracture during the baseline period. Further, we excluded conditions that may be associated with osteoporosis severity: patients whose index osteoporotic fracture was associated with car accident or high impact trauma (ICD 9 code, E810-E819, E881-E883, E8841) or those with diagnosis of Paget's disease (ICD 9 code, 731.0) or malignant neoplasm (ICD 9 code, 140-208) during the baseline period. Finally, we excluded patients with past history of DVT (ICD 9 code, 4511, 4512, 4519, 4532, 4534, 4538, 4539, 45181) or PE (ICD 9 code, 4151).

Exposure to osteoporosis drugs

During the study period, drugs reimbursed for osteoporosis patients in Taiwan were alendronate, calcitonin, and raloxifene. During the study period, alendronate was the only oral bisphosphonate reimbursed for patients with osteoporosis. Total supply in days and quantity of drugs were estimated from pharmacy claims originating from the inpatient and outpatient settings and contracted pharmacies of NHIRD. In the primary analysis, we adopted the on-treatment scenario, that is, patients were censored if they switched to other treatment groups after treatment initiation or were not persistent on their therapy (last date covered by drug plus 30 days, allowing for a 30-day gap between prescriptions). Patients were classified into the alendronate group, raloxifene or calcitonin nasal spray group according to the 1st exposure after their osteoporotic fractures. And, calcitonin was selected as the reference drug.

Outcomes and Covariates

The primary outcome of our study was all incident symptomatic VTE, including DVT and PE, in 3 treatment groups. DVT and PE were also evaluated separately as the secondary outcomes. The VTE events were identified from the inpatient and outpatient claims, and to avoid misdiagnoses, we only selected events which met all

the following criteria: (i) the discharge diagnosis was DVT or PE; (ii) the patient received a course of subcutaneous or intravenous anticoagulation therapy with unfractionated heparin or surgical thrombectomy during hospitalization and continued oral warfarin therapy after discharge; and (iii) a length of stay of at least 3 days, unless the patient died. We also selected outpatients who met the following criteria: (i) the principal diagnosis was DVT or thrombophlebitis; and (ii) the patient received a course of subcutaneous anticoagulation therapy with LMWH and continued oral warfarin therapy. The same criteria have been were employed in previous studies that investigating the VTE risk in Taiwan (20, 22). Patient demographic information was identified at treatment initiation and other covariates were determined by medical and pharmacy claims within 1 year before the index date. The following covariates were included in assessing the study outcomes: demographic characteristics (age, gender), income level (using insurance fee as the surrogate), osteoporosis-related factors (osteoporosis, kyphosis), fracture history (all non-vertebral fractures except than radius/ulna and hip fracture), major orthopedic surgeries (close and open reduction of fracture with internal fixation, joint replacement of the lower extremity and other procedures on the spine), co-morbid conditions that may increase fracture risk (Alzheimer's disease, asthma, diabetes, ischemic stroke, history of falls, rheumatic arthritis), comorbid conditions that could increase VTE risk (ischemic heart disease, chronic lung disease, ischemic stroke and intracerebral hemorrhage, degenerative and paralytic neurologic disease, varicose veins of the lower extremities) and co-medications that were associated with fracture risk(antiepileptics, β-Blockers, benzodiazepines, glucocorticoids, NSIAD/COX2 agents, hormone replacement therapy, SSRI, thyroid drugs and sleep/hypnotic agents).

Statistical analysis

Differences between alendronate vs. calcitonin and raloxifene vs. calcitonin in patient demographic information and other covariates were determined either by ANOVA or Pearson's chi-square test. Then, we used the multivariate Cox proportional hazard model to compare the relative VTE risk among different treatment groups. In the second analysis, the propensity score for each comparison group (aldendronate vs. calcitonin and raloxifene vs. calcitonin) was computed respectively, using multivariate logistic regression analysis that included all baseline covariates. Using the Greedy 5 → 1 digit technique, the comparison groups were then matched by the propensity score in a 1:1 ratio(23). Further, the Kaplan-Meier method was used to present event rates and time-to-event curves.

We performed a series of sensitivity and subgroup analyses to test the robustness of our findings from the main analyses. First, we extended the duration that patients received therapy to the last date covered by the drug plus 90 days. Second, in order to further observe sufficient effects from medications, we excluded short-term users if they did not have at least three prescriptions of the study drugs. Third, we further estimated the cumulative doses that patients received during the follow-up period in each treatment group according to the WHO defined daily dose (DDD), and cumulative doses were classified into 6 months (180 DDDs), 6 months to 1 year (180~365 DDDs) and above 1 year (>365 DDDs) equivalent. Forth, in order to account for healthy user bias, we examined our results in an intent-to-treatment scenario, by assuming patients' exposure to the treatment continued to death or end of follow-up (2009/12/31). Fifth, we examined the results in series subgroups, which were known to have different VTE risks: female subjects only, patients with osteoporosis diagnosis, different age and fracture risk subgroups, while excluding patients with varicose veins or those who had HRT. Finally, we examined our results using inpatient outcomes only.

2 Results

Baseline Characteristics of Osteoporosis drug users

From 2003~2007, we identified 80,993 new vertebral/hip fracture patients who had been exposed to osteoporosis drugs after a fracture occurred. After excluding 6,234 patients who had cancer or Paget's disease, 590 patients who had previous VTE events, 5,482 patients who had used osteoporosis drugs during the baseline period and 349 patients without complete insurance coverage/data, 66,985 patients remained in our study cohort. In our primary analysis, there were 25,443, 9,642 and 31,900 patients in the alendronate, raloxifene and calcitonin groups, respectively (Figure 1).

In general, the distribution of baseline characteristics was not even across the 3 treatment groups (Table 1). Calcitonin users tended to be older, had predominantly vertebral fracture, were less likely to have other non-vertebral fracture history but more likely to have used BZD, steroids, thiazides, and thyroid drugs. Alendronate and raloxifene users were more similar in age, comorbid conditions and co-medication exposure. The crude VTE rates were 0.42%, 0.40% and 0.37% in the alendronate, raloxifene and calcitonin group, respectively (Table 1). In order to account for the differences between groups in baseline characteristics, we further matched 20,489 patients in the alendronate and calcitonin groups and 8,034 patients in the raloxifene and calcitonin groups by the propensity score, respectively. After matching by propensity score, the distribution of baseline characteristics was even in the alendronate vs. calcitonin comparison and raloxifene vs. calcitonin comparison.

Incidence and risk of VTE for alendronate or raloxifene compared with

calcitonin

In the primary analysis, we did not find a significantly higher VTE risk among alendronate or raloxifene recipients as compared to calcitonin recipients (adjusted HR for alendronate: 0.84; 95%CI, 0.47-1.51; adjusted HR for raloxifene: 0.64; 95%CI, 0.33-1.28). Similar results could be found when we changed the outcome into DVT or PE only. Also, the differences in risk for VTE, DVT or PE were not significant after matching comparison groups by propensity score. In the multivariate Cox model, we found age and varicose veins were only two factors that were significantly associated with elevated VTE risk (adjusted HR for age: 1.02; 95%CI, 1.00-1.03; adjusted HR for varicose veins: 5.35; 95%CI, 1.29-22.11).

The incidence of VTE in alendronate, raloxifene and calcitonin groups was 11.2, 8.5 and 18.8 per 10,000 person-years (Table 2). When outcomes were analyzed with time-to-event methods, the Kaplan-Meier analysis did not find a significant difference between the groups in VTE rate during the 6 years follow-up period (Figure 2, P=0.3180, log rank test). There was neither a significant difference between the 3 groups in DVT or PE-only outcome (P=0.1711, DVT log rank test; P=0.8930, PE log rank test). Results of sensitivity and subgroup analyses were summarized in Table 3. Risk for VTE was similar in alendronate vs. calcitonin and raloxifene vs. calcitonin comparisons when we extended the follow-up by 90 days and excluded short-term users in the primary analysis. Similar patterns of results were found among comparison groups with different cumulative dose ranges, but with wider confidence intervals around the point estimates due to smaller sample size of subgroups. Moreover, no event was found in raloxifene recipients who received a 180~365 DDD cumulative dose. Consistent results were also found in the intent-to-treat analysis and in the subgroup analyses, including in patients with osteoporosis diagnosis, different non-vertebral or

hip fracture histories, female patients, patients previously diagnosed with varicose veins or who received HRT.

3 Discussion

This retrospective analysis found that the incidence of VTE in Taiwanese osteoporosis patients was low. And, the incidence and risk of VTE was similar across alendronate, raloxifene and calcitonin recipients in patients with osteoporotic fractures who were new to osteoporosis therapy. Age and patients comorbid with varicose veins were factors that significantly associated with elevated VTE risk. Consistent results were found in a series of sensitivity and subgroup analyses.

Our previous studies found the incidence of VTE in the Taiwan general population was 1.6 per 10,000 person-year, which was much lower than that in the US or UK populations (crude incidence rate ratio (IRR), 0.15) (20, 24). Nevertheless, the incidence of VTE in Taiwan increased dramatically when patients were aged over 50 years, which was the prevalent age of osteoporosis. And the incidence of VTE in Taiwan osteoporosis population is unknown. In 2010, Breart et al first compared the incidence of VTE between the osteoporosis and non-osteoporosis populations using General Practice Research Database in the UK (6). They reported that the osteoporosis population had a significantly higher VTE rate (56 per 10,000 person-year) as compared with the non-osteoporosis population (32 per 10,000 person-year). In addition, they found the incidence of VTE among alendronate recipients was 72 per 10,000 person-years. In our study, we included Taiwan osteoporotic fracture patients aged above 50 years and found the incidence of VTE among alendronate recipients in Taiwan was 11.2 per 10,000 person-years, which was only one-seventh of UK alendronate recipients (crude IRR: 0.14). Therefore, our study found when comparing Taiwan with Western countries, the IRR of VTE was similar in the general and osteoporosis population under treatment (crude IRR: 0.15, 0.14, respectively), which

confirmed that the incidence of VTE in Taiwan is only one-seventh of the Western countries. In addition to previous finding in a UK study, that there was no significant difference in VTE rates between treated and un-treated osteoporosis populations (6), our study further found no difference in VTE rates between alendronate, raloxifene and calcitonin recipients in Taiwan.

To date, three large studies have used the health insurance database to investigate the association between bisphosphonates and VTE (6, 18, 19), but employed different study designs and comparison groups. Two Danish register-based studies, either using retrospective cohort (19) or case-control (18) designs, found oral bisphosphonates including alendronate, did not have increased risk for VTE, as compared with age and gender-matched general population. Also, they failed to find a dose-response relationship between the use of alendronate and VTE (19). Moreover, results from a cohort study using GPRD found the risk of VTE in alendronate recipients was similar to the un-treated osteoporosis population (HR, 0.99; 95%CI, 0.80-1.23) (6). However, there were large differences in the VTE risk factors between the comparison groups in the above studies, and the exposure statuses during follow-up were unclear. In modern pharmacoepidemiology, selecting new users as the study population and using active controls may provide more unbiased and homogenous comparisons (25). In our study, we first selected new users of alendronate and adopted calcitonin recipients as the active control since there was no report of risk for VTE associated with calcitonin from pre-clinical and clinical studies and post-marketing data (7). We examined our results in the on-treatment scenario first, where the persistence of patients on their medications during the follow-up was more accurately depicted. We then matched alendronate and calcitonin recipients by propensity score, which minimized the likelihood of confounding by indication and enabled more homogenous comparisons (26). No significant difference in VTE risk between the alendronate and

the control group was found in the original and propensity-score matched cohort and on-treatment and intent-to-treat scenario. Furthermore, we did not observe a dose-response relationship between the use of alendronate and risk of VTE either. Therefore, our study further supports the findings from a previous study (6) that alendronate recipients did not have excess risk among the osteoporosis population, even in a population such as in Taiwan where the VTE rate was only one seventh of the Caucasians.

It is well-known that the use of raloxifene may increase VTE risk in postmenopausal women (7, 16, 17). Results from clinical trials and meta-analyses found that raloxifene users may have twice higher the risk of VTE (16, 17, 27) and 91% higher risk for PE as compared with placebo users in Western countries. However, related reports in Asian populations were limited. A short-term randomized controlled trial did not observe any VTE event in an Asian postmenopausal population during a 6-month treatment with daily raloxifene (28). In consistent with previous Asian study (28),we found the incidence of VTE among Taiwan raloxifene recipients was extreme low (8.5 /10,000 person-year), and no event occurred after consistently 3.5 years exposure to raloxifene. Further, we did not find an excessive risk of VTE among raloxifene recipients as compared with calcitonin recipients. Therefore, our results suggested that VTE risk may not be a concern when use of raloxifene in Taiwan osteoporosis population.

Although we extensively adjusted the results with multivariate and PS-matching models, and performed a series of sensitivity and subgroup analyses, there were several limitations and unmeasured confounders in our study. First, as we focused only on symptomatic VTE in our study, the incidence of VTE in the Taiwan osteoporosis population may have been underestimated. Patients with asymptomatic VTE or who died before an accurate diagnosis could be made were not captured in our study.

Nevertheless, using symptomatic VTE as the outcome may reduce the potential for misclassification bias. The definition of incident VTE event in our study was patients with VTE diagnosis who had previously received anticoagulant therapies, which may have provided more valid risk estimation. Second, there might exist some unmeasured confounders in the NHIRD, and there is no information on the severity of osteoporosis of patients in our cohort. However, all patients included in our cohort had experienced vertebral or hip fractures, which were consistent with the definition of severe or established osteoporosis by National Osteoporosis Foundation criteria (1). Also, data on socioeconomic factors were lacking, although we used the insurance premium paid as a surrogate for income level; the validity thereof is unknown. Furthermore, information about patients' lifestyle and behavior, such as body mass index, smoking status and travel histories, was not available. In spite of several limitations in our study, there were several strengths as well. First, our study was the first large scale one in Asia to assess the incidence and risk for VTE among the osteoporotic fracture population, which is known to have higher VTE risk. Second, the database we used (NHIRD) comprised over 99% of the Taiwan population, thus the osteoporotic cohort in our study had good generalizability. Third, we reported our findings with extended length of follow-up (maximum 6 years). Finally, we extensively included potential confounders in our database for adjustment, and further matched patients by propensity score based on these confounders, which minimized the potential bias from these factors.

Our study found the incidence and risk for VTE among the Taiwan osteoporotic fracture population was similar, regardless whether patients received alendronate, raloxifene or calcitonin treatment. Also, we found there were ethnicity-based differences in VTE incidence between Taiwan and Western countries; specifically, the VTE incidence was much lower in Taiwan than in Western countries, both in general

(20) and in the osteoporosis populations in our study. The results indicate that there was no significant difference in risk of VTE among Asian osteoporotic fracture patients receiving alendronate, raloxifene or calcitonin. Osteoporotic fractures have significant impact on mortality and future fracture risks, but they can be prevented with proper pharmacological treatments (1). Efforts should be made to ensure fracture patients receive secondary prevention and remain compliant with their therapies.

Figure 1 Study inclusion flowchart

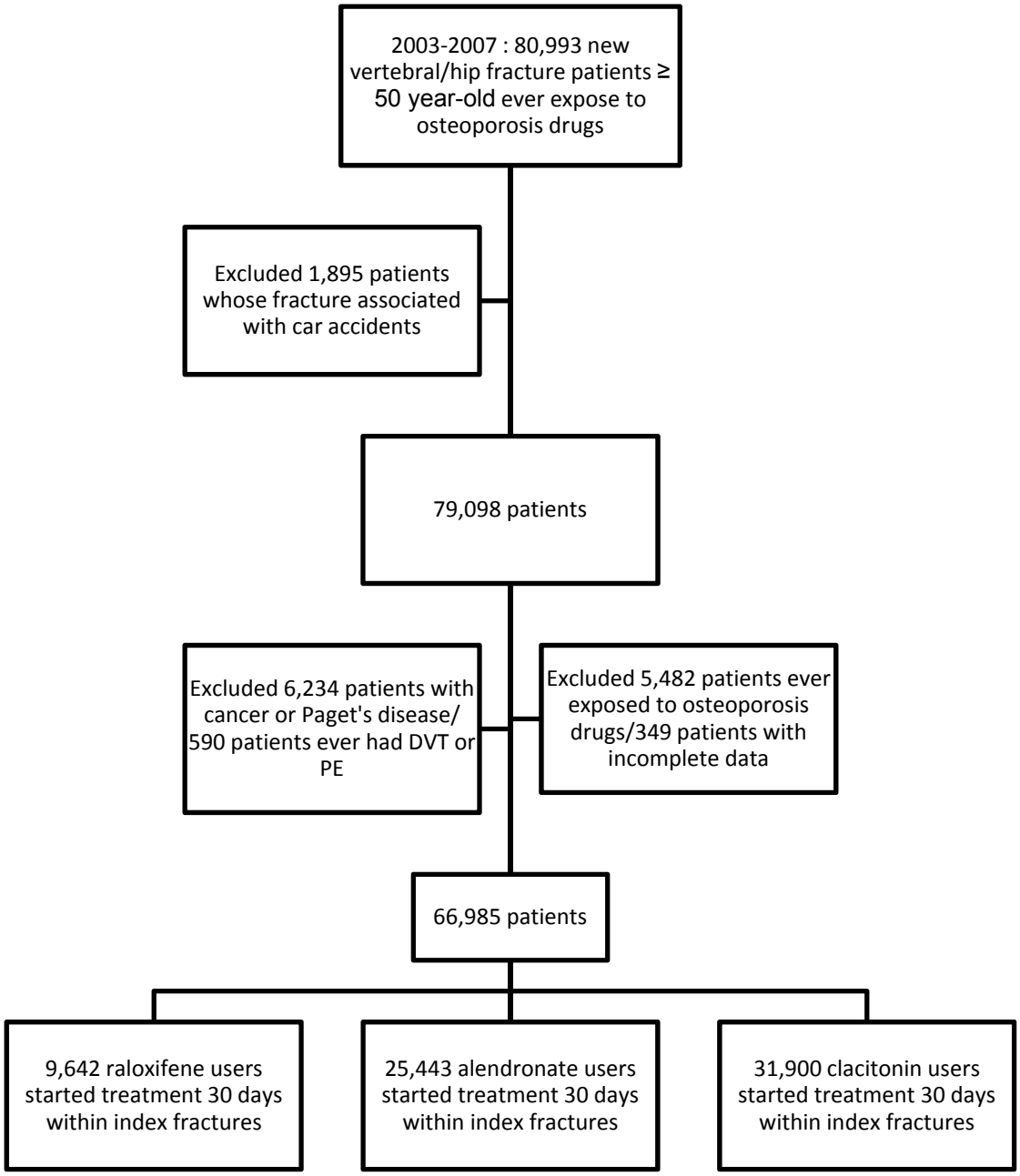
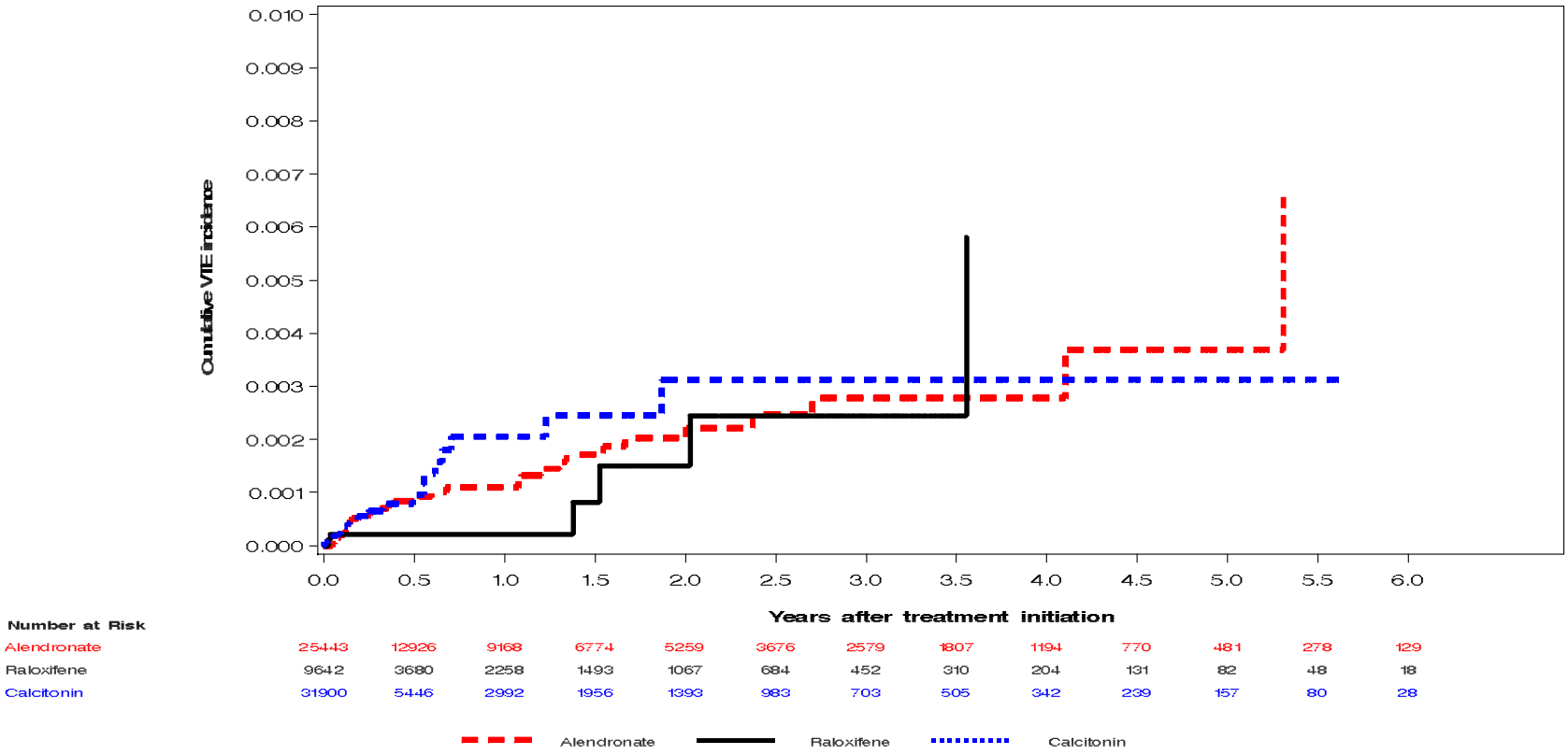


Figure 2 Kaplan-Meier Analysis for Risk of VTE



P for log rank test: 0.3180

Table 1 Baseline characteristics of new osteoporosis drug users

	Alendronate (N=25,443)	**Raloxifene (N=9,642)**	**Calcitonin (N=31,900)**	**P value**
Mean age, (SD), y	74.2 (9.6)	73.8 (9.7)	74.9 (9.5)	<0.0001
Gender (female),%	78.0	98.8	79.7	<0.0001
Index osteoporotic fracture				<0.0001
Hip, %	28.7	32.1	9.0	
Vertebral, %	71.3	67.9	91.0	
Comorbid conditions, %				
Osteoporosis	78.9	79.8	78.5	0.0193
Other non-vertebral fracture	19.9	18.5	15.8	<0.0001
Major orthopedic Surgery	55.9	23.2	20.9	<0.0001
Alzhelmer's disease	7.5	7.3	6.9	0.0576
DM	24.6	27.3	24.9	<0.0001
Parkinsonism	5.7	5.3	5.9	0.0458
Renal insufficiency	6.7	8.6	9.2	<0.0001
Hyperlipidemia	18.1	18.4	16.4	<0.0001
SLE	1.7	1.9	1.6	0.1556
Rheumatoid arthritis	3.5	3.9	3.2	0.0033
Hypertension	57.1	58.6	57.5	0.0455
Heart failure	8.4	9.1	10.3	<0.0001
Ischemic heart disease	23.6	22.4	25.0	<0.0001
Chronic lung disease	23.6	20.1	24.7	<0.0001
Ischemic stroke and intracerebral hemorrhage	10.3	9.5	10.2	0.0597
Degenerative and paralytic neurologic disease	18.0	17.3	18.0	0.2074
Varicose veins of lower extremities	0.6	0.5	0.6	0.9710

Table 1 Baseline characteristics of alendronate users (Continued)

	Alendronate (N=25,443)	**Raloxifene (N=9,642)**	**Calcitonin (N=31,900)**	**P value**
Co-medications,%				
Antiepileptic	8.8	8.5	8.8	0.5969
Beta blockers	27.1	28.7	28.5	0.0002
BZD	51.8	52.0	53.7	<0.0001
Glucocorticoids	27.5	25.3	29.5	<0.0001
HRT	3.5	3.9	3.2	0.0020
COX2	24.7	22.8	22.1	<0.0001
SSRI	3.5	3.5	3.4	0.9450
Thiazides	7.5	8.3	8.3	0.0005
Thyroid drugs	7.5	5.6	15.3	<0.0001
BMD	5.9	4.4	5.0	<0.0001
Income				<0.0001
Low	40.8	41.0	40.8	
Middle	24.1	17.9	25.4	
High	35.1	41.2	33.8	
Incident VTE, %	0.42	0.40	0.37	0.6993

*DM, diabetes mellitus; BZD, benzodiazepines; HRT, hormone replacement therapy; SSRI, selective serotonin reuptake inhibitors.

Table 2 Incidence and Risk of VTE of Osteoporosis Drugs Compared with Calcitonin

			Hazard ratio (95%CI)					
Outcome	**Event, N**	**Incidence rate /10,000 person-years**	**Unadjusted**	**P value**	**Adjusted M1***	**P value**	**PS matching**	**P value**
Venous thromboembolism								
Alendronate	31	11.2	0.76 (0.43-1.31)	0.3202	0.84 (0.47-1.51)	0.5581	0.64 (0.33-1.28)	0.2079
Raloxifene	6	8.5	0.53 (0.21-1.29)	0.1615	0.57 (0.22-1.45)	0.2358	0.59 (0.17-2.10)	0.4189
Calcitonin	24	18.8	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Deep Vein Thrombosis								
Alendronate	20	7.2	0.62 (0.32-1.18)	0.1339	0.67 (0.34-1.32)	0.2442	0.59 (0.26-1.34)	0.2047
Raloxifene	4	5.7	0.43 (0.15-1.28)	0.1301	0.45 (0.15-1.39)	0.1634	0.47 (0.10-2.15)	0.3247
Calcitonin	20	15.7	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-
Pulmonary Embolism								
Alendronate	11	4.0	1.08 (0.36-3.21)	0.1093	1.30 (0.42-4.08)	0.6494	0.79 (0.23-2.76)	0.7146
Raloxifene	2	2.8	0.75 (0.14-3.90)	0.0116	0.87 (0.16-4.80)	0.8755	1.06 (0.10-11.85)	0.9632
Calcitonin	5	3.9	1.00 (reference)	-	1.00 (reference)	-	1.00 (reference)	-

* Adjusted for all variables in Table 1.

Table 3 Sensitivity and subgroup analysis

	Participants, N	Alendronate	Participants, N	Raloxifene
Primary analysis	25,443	0.84 (0.47-1.51)	9,642	0.57 (0.22-1.45)
+90	25,443	1.17 (0.69-1.99)	9,642	0.89 (0.40-1.97)
Excluded short-term users	17,737	0.69 (0.37-1.26)	5,838	0.47 (0.17-1.29)
Cumulative doses				
≤180 DDDs	15,904	1.54 (0.79-3.00)	7,152	0.82 (0.27-2.50)
180~365 DDDs	3,618	0.73 (0.08-6.47)	1,193	--- †
>365 DDDs	5,921	0.31 (0.05-1.78)	1,297	0.31 (0.04-2.85)
Intent-to-treat scenario	25,443	1.23 (0.94-1.62)	9,642	1.18 (0.81-1.71)
Index osteoporotic fracture				
Vertebral fracture	18,152	0.76 (0.40-1.45)	6,545	0.44 (0.13-1.51)
Hip fracture	7,291	1.07 (0.22-5.25)	3,097	0.88 (0.14-5.77)
Fracture history				
No fracture history	20,376	0.59 (0.30-1.14)	7,856	0.59 (0.22-1.52)
With osteoporosis diagnosis	20,070	0.71 (0.37-1.36)	7,697	0.52 (0.19-1.46)
Stratified by age groups				
50-65 yr	3,337	0.40 (0.02-7.59)	1,493	0.59 (0.16-2.19)
65-80 yr	14,043	0.49 (0.22-1.09)	5,231	0.46 (0.15-1.45)
≥80 yr	7,732	1.99 (0.70-5.63)	2,836	0.94 (0.17-5.11)
Female only	19,832	0.67 (0.36-1.28)	9,530	0.50 (0.20-1.28)
Excluded patients with Varicose veins of lower extremities	25,303	0.83 (0.46-1.50)	9,591	0.59 (0.23-1.50)
Excluded patients with HRT	24,558	0.91 (0.50-1.66)	9,263	0.62 (0.24-1.60)
Inpatients only	25,443	0.68 (0.17-2.78)	9,642	0.73 (0.18-2.97)

* Adjusted for all variables in Table 1.

† No VTE events in raloxifene recipients.

4 Reference

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附件五

國科會補助專題研究計畫出席國際學術會議

心得報告

日期：2013 年 10 月 22 日

計畫編號	NSC101－3629－B－006－001－		
計畫名稱	台灣骨質疏鬆族群於醫療利用及用藥安全之性別差異		
出國人員 姓名	錢敘芝	服務機構 及職稱	成功大學臨藥科技所 /博士班研究生
會議時間	102 年 08 月 24 日至 102 年 08 月 28 日	會議地點	加拿大蒙特婁
會議名稱	(中文)第二十九屆藥物流行病學及風險管理國際研討會 (英文)29th International Conference on Pharmacoepidemiology and Therapeutic Risk Management		
發表題目	(中文)台灣晚期胰臟癌患者憂鬱症治療 (英文)　Management of Depression in Taiwan: Unmet needs in Advanced Pancreatic Cancer Patients?		

一、參加會議經過

大會議程共包含 2 天 pre-conference education sessions 及 3 天 conference session。

8/24 – 上午參加 educational course 中的"introduction to pharmacoepidemiology"，上課內容包含 cohort studies 及 case-control studies 的研究設計以及可能產生的 bias 及 confounding；下午"using pharmacoepidemiology database resources to address drug safety research"課程，則說明利用登錄或申報資料庫進行藥物流行病學研究之實例，以及如何選擇適當資料來源進行研究，目前加拿大有 66 歲以上老年人的健保資料類似台灣全民健保資料，而隨科技的進步，如何串連不同國家資料進行研究也在課堂上說明。

8/25 – 上午參加”comparative effectiveness research: methodologic challenges of newly marketed medical products”，上課內容先說明為何在新上市藥品仍需要進行療效對照研究，主要是由於一般新藥上市前的臨床試驗要求以無用藥組(placebo)為對照組，用於證實新藥之臨床療效，另外，多數臨床試驗會侷限於少數患者，因此較缺乏與其他已上市藥品之比較，而美國 Johns Hopkins University 的 Dr. Segal 列出二十項應該進行 comparative effectiveness research 的情況，除此之外，美國哈佛大學 Dr. Schneeweiss 以實例說明新上市藥品進行療效對照研究之方法學。下午”a state-of-the-art review of benefit-risk assessment and risk communication practice” 討論 benefit-risk assessment 的方法及其他國家進行 benefit-risk assessment 的成果。

8/26 - 參與大會正式會議，首先由國際藥物流行病學會資深成員 Dr. LeLorier 及 Dr. Begaud 以互動的方式討論議題” Two Solitudes: are we talking to each other?”。接著參加不同的 concurrent session，包含方法學”back to the future” methods in time”，(1) flexible marginal structural cox models for estimating cumulative effect of time-dependent treatment on the hazard (2) de-constructing a marginal structural model: effects of follow-up duration on stabilized weights and findings in a study of myocardial infarction risk in hemodialysis patients (3) evaluating newly-marketed medications with a high-demensional disease risk score estimated in a historical cohort (4) using predicted probabilities of exposure and outcome to assess confounding (5) relative performance of approaches handling immortal person-time in comparative effectiveness research: a simulation study (6) misclassification in assessment of diabetogenic risk using laboratory-enhanced claims data。中午參加學生會議 student council 討論明年度在台灣舉辦大會時之事宜。下午參加 concurrent session，為方法學”methods in CER”，(1) Comparing effectiveness estimates from randomized and nonrandomized studies, using subgroup analyses and individual patient data (2) information gained by linking administrative claims

to structured electronic health record data in a statin comparative effectiveness study (3) imaging and electronic health record (EHR) data for comparative effectiveness research (CER): experience from a tertiary care hospital (4) preference-based instrumental variable methods in the comparative effectiveness of osteoporosis (5) comparing propensity score estimation using logistic regression and generalized boosted regression in a real-world comparative effectiveness study of glaucoma therapies (RiGOR) (6) Identifying appropriate comparisons for comparative effectiveness research (CER)。另外大會安排的 Plenary session 是討論 Natalizumab (Tysabri)與發生 progressive multifocal leukoencephalopathy (PML)的個案，討論內容包含(1) describe the clinical course of multiple sclerosis and how Tysabri is used (2) describe the pathogenesis /epidemiology of PML as a risk of Tysabri treatment (3) describe risk stratification of PML as a guide to Tysabri treatment (4) describe the patient/regulatory considerlations around Tysabri and PML。

8/27- 參與 concurrent session，" Pediatrics" (1) risk of suicide and suicide attempt associated with atomoxetine compared to central nervous system stimulant treatment (2) pediatric sleep disorders: trends, treatment and association with adolescent depression (3) risk of febrile seizure following inactivated influenza vaccine and concomitant vaccines (4) antibiotics and hepatotoxicity in pediatric primary care: a case-control study using electronic healthcare databases (5) growth impairment and risk of cancer and cardiovascular disease in children (6) effectiveness of rotavirus vaccines in preventing rotavirus gastroenteritis related hospitalizations in privately-insured US children, 2007-2010。"Methods" (1) reporting of instrumental variable analyses in comparative effectiveness research (2) considerations for creating a calendar time instrumental variable in specific settings of nonexperimental comparative effectiveness research (3) improvement of 1:M matching using an

adaptive algorithm: proof of concept (4) comparison among EU-ADR, OMPO, Mini-Sentinel and MATRICE strategies for data extraction and management (5) comparing disease risk scores with propensity scores for confounding control when evaluating newly introduced treatment therapies (6) evidence of free sample use among new users of branded statins。下午時段的 plenary session 主題為"the patients voice in benefit & risk"，討論病患自我通報方式，如何評估藥品之療效及安全性。

8/28 – 參加 concurrent session，"sexy hormones" (1) oral glucocorticoids and the risk of incident type II diabetes mellitus in patients with rheumatoid arthritis, a retrospective cohort study (2) venous thromboembolism in users of a 24-day regimen of a combined oral contraceptive compared to conventional 21-day regimens: final results from the INAS-OC study (3) the safety of oral contraceptives in adolescents (4) combined oral contraceptive and venous thromboembolism-time matters (5) the implications of 'off-label' use in primary care in England: an example from a post-marketing cohort study (6) menopausal hormone therapy and risks of cardiovascular events and mortality in female statin users-a population based register study。另外參加 workshops "challenges in studying drug-induced liver injury in pharmacoepidemiology data sources，討論如何定義藥品引起的肝傷害，大多數仍必須倚賴實驗數據的證實。下午分別參與"self-controlled studies" 的研究方法以及"sticky treatment &sticky outcomes" 的討論。中午時段與國外學者討論發表壁報之內容。大會最後一天安排的 Hot Topics session 主題為"considering the safety of compounded drugs" 主要討論 methylprednisolone 因為配製污染導致病患產生腦膜炎的個案，從個案發生，如何確認因果關係，NEJM 主編的看法至減少風險的策略等。由於明年大會在台灣舉行，因此由台灣主辦單位代表高雅慧教授，於會議結束前宣傳相關事宜。

二、與會心得

1. 參加會議前二天所舉辦的教育訓練課程，不但可以複習之前所學的方法，亦可以知道最新的研究方法。
2. 在參加會議不同的 concurrent session，聽到世界各國研究學者的研究成果，以及會議上各學者的討論，可激發研究方向的思考，並且可從中學習不同國家的研究資源及方法。
3. Workshops 的討論，聽到不同學者對相同主題作深入的討論，具有互相學習的意涵。
4. 於會議中發表自己的研究成果，與國外學者互相討論，不但可以在研究方法及結果上有交流討論，亦可增加台灣研究在國際上的曝光率。

三、發表論文全文或摘要

Management of Depression in Taiwan: Unmet needs in Advanced Pancreatic Cancer Patients?

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Background

Although depression is one of the strongest determinants of health related quality of life, it is likely to be under-reported by patient and under-diagnosed by physicians[1]. The information on the management of depression in pancreatic cancer patients in Taiwan is not yet available, studies using the National Health Insurance Research Database (NHIRD) may help to understand how depression is diagnosed and treated in these patients.

Objectives

To assess the clinical management of depression and prescription patterns of antidepressants.

Methods

Design and Setting

Firstly, a cross sectional study was conducted in a tertiary referral center. All advanced pancreatic cancer (pancreatic adenocarcinoma) patients from September 2012 to January 2013 were invited. To assess depression, the pharmacist interviewed patients by two stem questions (2Q), which is recommended by Depression in Cancer Care Consensus Group[2]. The diagnostic validity of 2Q, weighted sensitivity and specificity of 2Q was 95.6% (95% CI=89.0% to 99.3%) and 88.9% (95% CI=79.0% to 96.0%), respectively.

Clinicians also independently evaluated if these patients had depression.

Secondly, to explore the nationwide scenario, we examined the prescribing patterns of anti-depressants in pancreatic cancer patients using a 1-million randomly sampled beneficiaries' data in 2010 from Taiwan's NHIRD.

We further confirmed the diagnose of pancreatic cancer (ICD9-CM-code: 157) with the Registry for Catastrophic Illness Patient Database, a subpart of the NHIRD.

The prevalence of depression (ICD9-CM-code: 293.83, 296.2,296.3, 300.4, 309, 309.1, 309.28, 311) and utilization of depressants (ATC-code: N06A) were estimated.

Exposures or interventions

None.

Statistical analysis

We defined the prevalence of depression as the number of patients diagnosed divided by the total number of patients in a given period. The prescription rate was defined as the number of patients receiving anti-depressants divided by the total number of patients in a given period. We examined the bivariate association of 2Q and physician diagnosed depression with Fisher's exact test. Exact methods were used to calculate 95% CIs. All analyses were performed with SAS 9.3 software.

Results

We identified 49 advanced pancreatic cancer patients (Table 1). Among the eligible patients, 31 (63.3%) were diagnosed as depression by clinicians, while 41 (83.7%) identified by the 2Q. The concordance of clinicians' diagnosis and 2Q is 0.45 (p=0.0041). None of the patients were taking or prescribed antidepressants at the time of interview. Paroxetine was prescribed to one patient at a week after our interview.

With NHIRD, in 87 pancreatic cancer patients, 5 (5.8%, 95% CI=1.9%-12.9%) were recorded with depression, and 16 (18.4%, 95% CI=10.9-28.1%) were prescribed with anti-depressants. 4 depressive pancreatic cancer patients were prescribed with anti-depressant(s) (Table2).

Conclusions

Our findings suggest that remarkable discrepancies between clinical observation and database findings indeed existed. Unmet needs of depression management in patients with pancreatic cancer require further investigation.

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Table1. Invited advanced pancreatic cancer patients characteristics of in NCKUH.

	Eligible Patients (n=49)
Characteristics	**Patient Number (%)**
Male sex	**27 (55.10)**
Age, years	
<50	**3 (6.12)**
50-59	**16 (32.65)**
60-69	**17 (34.69)**
70-79	**10 (20.41)**
≥80	**3 (6.12)**
Marital status	
Married	**37 (75.51)**
Single	**3 (6.12)**
Widowed/divorced	**9 (18.37)**
ECOG performance status	
≤1	**34 (69.39)**
2	**10 (20.41)**
3	**2 (4.08)**
4	**3 (6.12)**
Intervals of diagnose to interview	
<30 days	**9 (18.37)**
30-79 days	**9 (18.37)**
90-179 days	**12 (24.48)**
180-364 days	**8 (16.33)**
≥365 days	**11 (22.45)**
Pancreatic cancer stage*	
IIb	**7 (14.29)**
III	**14 (28.57)**
IV	**28 (57.14)**
Surgery for primary tumor	
Yes	**27 (55.10)**
No	**22 (44.90)**
Chemotherapy	
Adjuvant	**45 (91.84)**

Gem	**25**
Gem+ continuous infusion 5-FU	**10**
Gem + 5-FU/leucovorin/oxaliplatin	**7**
Continuous infusion 5-FU	**2**
TS-1	**1**
MM398-based	**6**
Chemoradiation	**13 (26.53)**
RT+Gem	**13**
Pain	
Yes	**35 (71.43)**
No	**14 (28.57)**
Anxiolytics, Hypnotics & Sedatives	**12 (24.49)**
Lorazepam	**3**
Alprazolam	**2**
Fludiazepam	**1**
Estazolam	**4**
Zolpidem	**3**
Comorbidity	
0	**7 (14.29)**
1	**18 (36.73)**
2	**10 (20.41)**
≥3	**14 (28.57)**

Abbreviations: ECOG: Eastern Cooperative Oncology Group; Gem: gemcitabine; 5-FU: fluorouracil; RT: radiation therapy; TS-1: tegafur & gimeracil & oteracil .

*By the American Joint Committee on Cancer (AJCC) tumor/node/metastasis (TNM) staging criteria for adenocarcinoma of the pancreas[3].

Table2. Advanced pancreatic cancer patients characteristics in NHIRD.

Characteristics	Eligible Patients (n=87) Patient Number (%)
Male sex	**46 (52.87)**
Age, years	
<50	**14(16.09)**
50-59	**16(18.39)**
60-69	**21(24.14)**
70-79	**25(28.74)**
≥80	**11(12.64)**
mean±sd	**63.33±15.26**
Depression	
Yes	**5(5.75)**
No	**82(94.25)**
Antidepressant	
Yes	**16 (18.39)**
No	**71 (81.61)**
Antidepressant received	
Imipramine	**5 (31.25)**
Fluoxetine	**1 (6.25)**
Paroxetine	**1 (6.25)**
Sertraline	**1(6.25)**
Escitalopram	**1(6.25)**
Moclobemide	**1(6.25)**
Trazodone	**2(12.5)**
Mirtazapine	**3 (18.75)**
Venlafaxine	**1 (6.25)**

四、建議

1. 藥物流行病學之研究，不論是在藥品療效或安全性之研究皆是以病患用藥安全為主軸，而維護藥品用藥安全，醫療主管單位的參與是不可或缺的，例如美國 FDA、歐盟 EMEA 等皆每年參與國際藥物流行病學會，希望國內衛生主管單位可以有更多人參加，不但可以了解藥物流

行病學之研究方法以及國外政策擬定之作法，更可以與國外決策單位作交流。

2. 國內健保資料庫是包含 99%以上全人口的就醫資料，已有許多學者以其為主要研究材料，因此明年在台灣舉辦第三十屆國際藥物流行病學，希望國內有更多人可以參與會議，學習更多研究方法。

五、攜回資料名稱及內容

1. 29th International conference on pharmacoepidemiology and therapeutic risk management-Final program 包含此次大會行程及會場位置
2. 29th International conference of pharmacoepidemiology and therapeutic risk management-List of Attendees 包含此次大會與會人士的姓名、單位以及連絡方式(e-mail)

六、其他

無

國科會補助計畫衍生研發成果推廣資料表

日期:2013/10/22

國科會補助計畫	計畫名稱: 台灣骨質疏鬆族群於醫療利用及用藥安全之性別差異
	計畫主持人: 高雅慧
	計畫編號: 101-2629-B-006-001- 學門領域: 性別主流科技計畫

無研發成果推廣資料

101 年度專題研究計畫研究成果彙整表

計畫主持人：高雅慧	計畫編號：101-2629-B-006-001-
計畫名稱：台灣骨質疏鬆族群於醫療利用及用藥安全之性別差異	

成果項目			量化			單位	備註（質化說明：如數個計畫共同成果、成果列為該期刊之封面故事...等）
			實際已達成數（被接受或已發表）	預期總達成數(含實際已達成數)	本計畫實際貢獻百分比		
國內	論文著作	期刊論文	0	0	100%	篇	
		研究報告/技術報告	0	0	100%		
		研討會論文	0	0	100%		
		專書	0	0	100%		
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力（本國籍）	碩士生	0	0	100%	人次	
		博士生	1	1	100%		培育一名博士生畢業。
		博士後研究員	0	0	100%		
		專任助理	2	2	100%		增加兩名專任助理就業機會。
國外	論文著作	期刊論文	0	1	100%	篇	目前已有一篇研究論文投稿至 Journal of Clinical Endocrinology & Metabolism，獲得 revision 的機會，目前正在修改中。
		研究報告/技術報告	0	0	100%		
		研討會論文	1	1	100%		本研究之結果獲得國際藥物流行病學會年會接受、口頭發表（oral presentation, 2013 International Conference on Pharmacoepidemiology）。
		專書	0	0	100%	章/本	
	專利	申請中件數	0	0	100%	件	
		已獲得件數	0	0	100%		
	技術移轉	件數	0	0	100%	件	
		權利金	0	0	100%	千元	
	參與計畫人力	碩士生	0	0	100%	人次	

	（外國籍）	博士生	0	0	100%		
		博士後研究員	0	0	100%		
		專任助理	0	0	100%		
其他成果 (無法以量化表達之成果如辦理學術活動、獲得獎項、重要國際合作、研究成果國際影響力及其他協助產業技術發展之具體效益事項等，請以文字敘述填列。)		無。					

	成果項目	量化	名稱或內容性質簡述
科教處計畫加填項目	測驗工具(含質性與量性)	0	
	課程/模組	0	
	電腦及網路系統或工具	0	
	教材	0	
	舉辦之活動/競賽	0	
	研討會/工作坊	0	
	電子報、網站	0	
	計畫成果推廣之參與（閱聽）人數	0	

國科會補助專題研究計畫成果報告自評表

請就研究內容與原計畫相符程度、達成預期目標情況、研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）、是否適合在學術期刊發表或申請專利、主要發現或其他有關價值等，作一綜合評估。

1. 請就研究內容與原計畫相符程度、達成預期目標情況作一綜合評估

■達成目標

□未達成目標（請說明，以 100 字為限）

□實驗失敗

□因故實驗中斷

□其他原因

說明：

2. 研究成果在學術期刊發表或申請專利等情形：

論文：□已發表 ■未發表之文稿 □撰寫中 □無

專利：□已獲得 □申請中 ■無

技轉：□已技轉 □洽談中 ■無

其他：(以 100 字為限)

目前已有一篇研究論文投稿至 Journal of Clinical Endocrinology & Metabolism ，獲得 revision 之機會。

3. 請依學術成就、技術創新、社會影響等方面，評估研究成果之學術或應用價值（簡要敘述成果所代表之意義、價值、影響或進一步發展之可能性）(以 500 字為限)

本研究發現，新發生骨鬆骨折族群，於醫療利用情況與未來骨折再發之風險上，存有性別差異。女性較男性易接收到骨鬆骨折之治療、時機點亦較早。不過，不論男性或女性，治療比例仍然偏低。此外，雖然女生骨鬆骨折再發之風險較男性為高，但是此現象在骨折發生後三年出現逆轉，暗示男性治療比例的偏低仍然會對未來骨鬆骨折發生有顯著地影響。另一方面，本研究發現骨鬆骨折族群中，發生靜脈栓塞的比例，女性較男性高。儘管如此，使用 alendronate 或 raloxifene，相較於 calcitonin，不會增加靜脈栓塞發生之風險。

根據本研究結果，衛生主管機關以及醫療專業人員，應該更加注意發生骨鬆骨折病患，發生骨折後接受治療之情況。特別是男性，治療比例顯著較女性為低。妥善地制定政策及相關衛教，對於增加男性病患之病識感與治療意願是很重要的。於藥物安全性方面，本研究發現目前之骨鬆藥品並不會增加靜脈栓塞風險，此結果可供醫師臨床上治療選擇之參考。