出國報告（出國類別：國際會議）

參加 2022 38th ICPE annual meeting

服務機關：國立成功大學醫學院附設醫院
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摘要

本次參加第三十八屆國際藥物流行病學學術研討會，會議地點在丹麥的哥本哈根城市，由於許多歐美國家已開放邊境，此次研討會除了pre-conference部分有開放線上參與，其餘皆是實體參與，現場有近1500人與會者來自52個國家，有1565篇摘要發表，台灣佔約50篇。大會議程如同往年有2天pre-conference education sessions及3天conference sessions。在education sessions主要介紹藥物流行病學的概念及研究方法，包含不同的研究設計及主題，也有進階及新穎的方法學或研究工具說明，可了解國外的發展方向。第3天為正式會議開始，議程有keynote、plenary presentation、oral presentation、symposium及poster presentation，因為covid-19感染是全球性，所以今年也有許多主題與covid-19疫苗安全或是治療有關。此次共指導5篇論文入選為poster presentation，其中二篇為本院藥師發表。今年的論文在大數據分析也有許多不同面向，在現場與其他學者交流討論，收獲豐富。國外的與會者大多的背景是醫師，但台灣較少醫師投入這個領域，另外，衛生主管機關的參與是相當重要的，尤其是現在real-word evidence是世界的潮流，國內需有更多成員參加此類會議，與國際接軌。

目次

一、 本文

(一) 出國目的：

本次出國為參加第38屆ICPE annual meeting，指導學生於會中發表論文結果。

(二) 參加會議過程：

大會議程共包含2天會前教育課程及3天正式會議，前兩天的pre-conference education sessions從基礎的藥物流行病學課程如藥物流病的基本概念與研究方法介紹，到進階的課程內容均有安排。主題囊括多種研究領域，包含服藥順從性、因果關係推論及機器學習課程等等都有。學生們可利用此密集授課之教育課程溫故知新，也可以根據有興趣的部分進行選修聆聽，部分課程更以工作坊方式進行，讓學生們透過實作將講授內容內化，學以致用。

8/26-8/28是正式會議，此次會議共有1500多位到現場參加會議，400多人線上參與，首次參加者高達900多人、abstract投稿數量創歷年新高，此次成大臨藥所也共有15位師生參加，聲勢浩大。

參與此次會議的成大臨藥所師生合影

照慣例，大會均會依據當年度就熱門的主題安排幾場重要演講：

1. 8/26 Keynote Plenary: Strategies for successful mass vaccination rollout: balancing science, politics, communication and trust。演講者為丹麥衛生局局長 Søren Brostrøm，他也是一位婦產科醫師，演講的內容是在探討covid-19疫苗的安全性，從臨床醫師及政策決定者的角度，如何看待疫苗施打的議題，丹麥當局以科學證據，並且公開透明的跟民眾說明，確實值得我們學習。
2. 8/27 Plenary Session: Updates from the COVID-19 pharmacoepidemiological battlefield: recent victories and battles ahead。分別由四位講者回顧COVID-19對全球造成重大的影響，以及未來可能面臨的挑戰，同時藥物流行病學學會應用real world evidence的方法在 COVID-19 大流行的許多貢獻，尤其是醫療部分。
3. 8/28 Hot topic: How can we mitigate publication of poorly conducted RWE studies? 自2019年開始COVID-19造成的死亡，讓大家迫切需

要各種COVID-19治療效果的數據，許多期刊放寬有關科學審查和嚴謹性的標準，形成“pandemic-related research waste”現象。雖然RWE已被認同是實證的參考，也有許多實例被應用作為決策的支持，因此，講者再次說明在執行RWE相關研究時應注意的事項，包含研究設計、資料來源、分析方法及報告等面向，皆須是適當且合理，以免不適當使用數據和方法而造成不良影響。

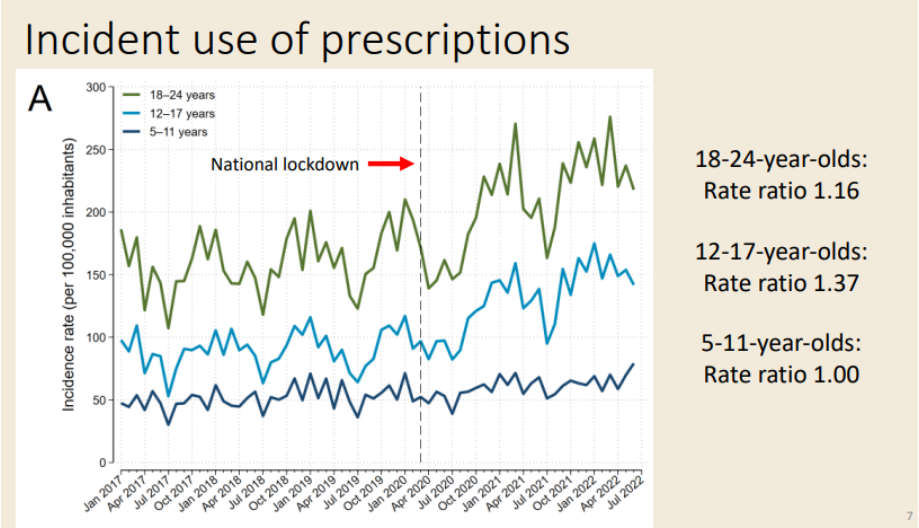
會議期間，參加了許多有興趣的symposium：

1. Methodological Challenges in Assessing the Impact of Digital Technologies on Patient Adherence：在評估藥品療效及安全性，如何確認藥品順從性相當重要，這個議題是採小組討論，分別就三個方向討論: (1) What are the key knowledge gaps? How can pharmacoepidemiology contribute? What aspects of adherence do you want to investigate? Which study designs can be used? (2) Where do we find the data? How to define the right outcomes to measure adherence? How can we identify users of technologies? (3) How do we address bias and confounding in studies of digital technologies in medication adherence?

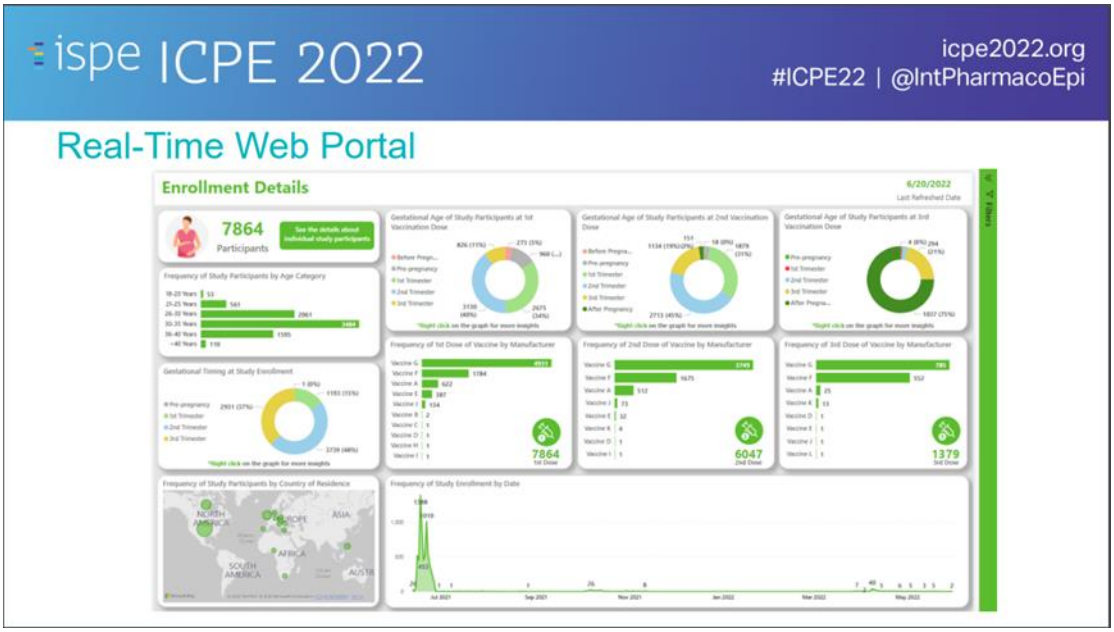
2. It Takes a Village: Strategic Global Collaborations to Advance RWE Within ISPE，在 ISPE 的 RWE 工作小組一直努力建立全球對 RWE 的價值及信任，此次議題原本有 5 位講者，但現場實際只有四位，內容說明三個面向：(1) Update the society on RWE Task Force achievements and encourage member involvement with future deliverables. (2) Illustrate how the work of the RWE Task Force members is enriched through strategic collaborations with well

established external organizations. (3) Showcase how the RWE Task Force stepped up to meet challenges related to COVID-19 research through novel strategic collaborations.

3. Increasing Use of Antidepressants, Hypnotics and Psychostimulants During the COVID-19 Pandemic Among Danish Children, Adolescents, and Young Adults：丹麥學者藉由登錄的資料分析在 covid-19 疫情期間，青少年族群使用精神相關用藥情形，在 12 歲以上的青少年使用量確實都有增加的趨勢，尤其是在疫情嚴重鎖國之後，結果如下圖所示，



4. Covid-19 Vaccine use during pregnancy: accelerating innovative evidence generation platforms to meet current and future challenges。演講內容分享一個創新、數位化且具全球性懷孕婦女施打疫苗的登錄系統C-VIPER (NCT04705116)，包含COVID-19疫苗，以Real World Evidence (RWE) 的研究設計。根據 HA 和Ethics Committee (EC) 的要求（包括中低收入國家的要求）實施統一的計畫內容、執行方法、統計分析和報告。初步收案結果如下圖所示。



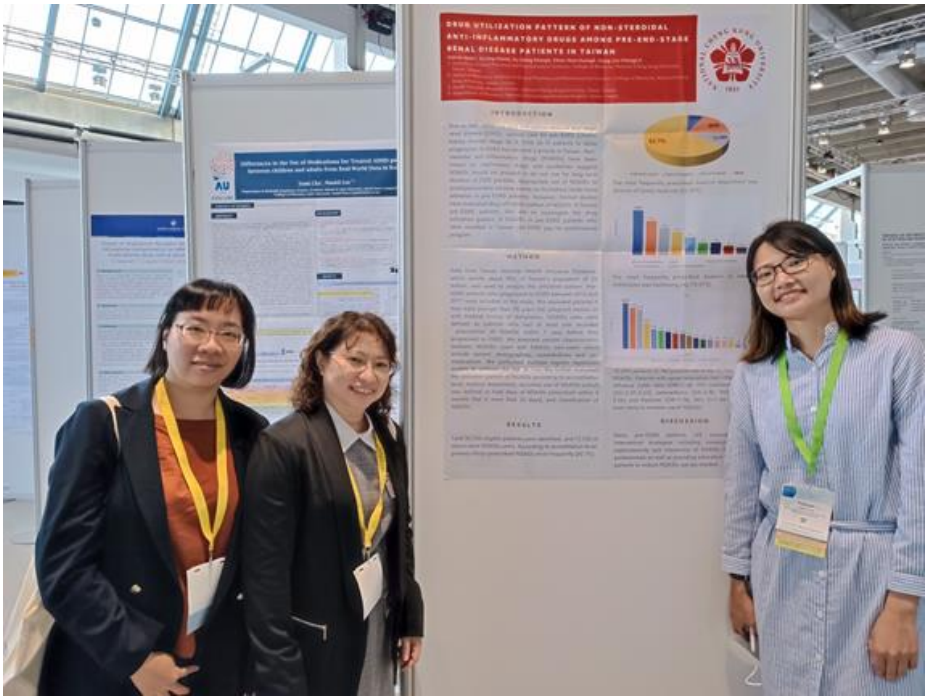
esentations:會議中安排多個口頭報告，報告者多為來自世界各地的學生，主題包含多種領域。除了可以了解目前大家的研究主題與進展以外，也可以參考別人如何呈現自己的研究成果。通過及時的Q&A，了解其他學者對自己研究的建議為何，有助於未來的研究。

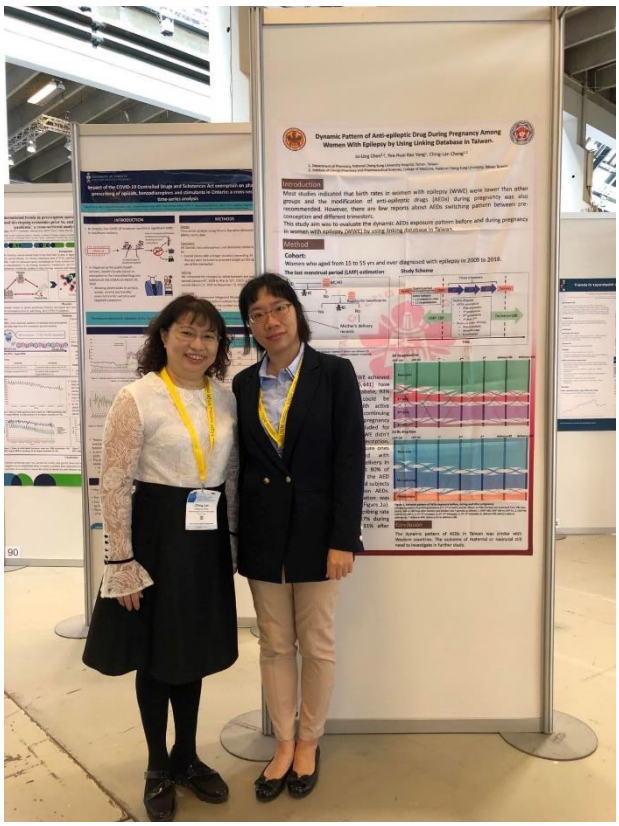
6. Poster sections:今年投稿件數很多，壁報展出內容也很多元，不過有些作者可能疫情沒有到場，但現場和壁報作者交流是一件相當愉快的經驗，不但可以討論對方的研究內容，還可以順便介紹台灣。共指導5學生進行壁報發表，發表題目如下表

	題目
1	Dynamic Pattern of Antiepileptic Drug During Pregnancy Among Women With Epilepsy by Using Linking Database in Taiwan
2	The Risk of Serious Infection in Crohn's Disease Patients Treated with Biologics: An External Comparator Cohort Study.
3	Drug Utilization Pattern of Non-Steroidal Anti-Inflammatory Drugs Among Pre-End-Stage Renal Disease Patients in Taiwan.
4	Comparative Safety of Beta-Blocker and Calcium Channel Blockers in

	Patients with Chronic Obstructive Pulmonary Disease and Atrial Fibrillation: A National Population Cohort Study in Taiwan.
5	Prescription Pattern of Empirical Antibiotic Used and The Factors Affecting Death in Children with Bacteremia in Taiwan

相關活動照片如下圖，論文摘要如附錄所示。





與指導學生於壁報前合影

7. Academic council: 學界的交流也是ISPE的其中一環，不過這次參加的國家只有4個，所以快速投票決定下屆的會長。
8. Student council: ISPE非常重視學生的發展與交流，成大的學生參與此council的人數最多，會中投票由成功大學臨藥所博士生擔任下一屆chair，活動照片如下圖。

(三) 參加會議的心得：

國際藥物流行病學會(ISPE) 是一個成立三十多年的國際組織，參加的會員包含全球 50 個國家以上，有來自於製藥行業、學術機構、政府機構、非營利和營利性私人組織各領域，會員有流行病學、生物統計學、醫學、護理學、藥理學、藥學、法律、衛生經濟學和新聞學等背景，其中以醫藥界為最多。ISPE 的成立宗旨是希望提供一個可以公開交換科學信息以及制定藥物流行病學領域的政策、教育和宣傳的全球論壇，包括藥物警訊、藥物利用研究、有效性比較審查和治療風險管理等方面。

ICPE 為 ISPE 重要的年度大會，每年 ICPE 皆會邀請知名的學者，針對特定主題安排演講，今年的主題當然會與 COVID-19 相關，並特別強調如何確保 RWE 的可信度。由於是實體的會議，會議安排不同主題的 symposium，讓與會者可以了解世界各國研究學者的研究成果與方向;在口頭報告也可以與作者進行交流討論，建立合作管道。除了學術交流外，ISPE 相當重視傳承，所以在正式會議的前二天安排了教育訓練課程，從基礎的研究設計及方法讓初學者得以入門學習，也會安排進階課程，讓大家可以更新研究設計或統計方法。藥物流行病學的研究主要著重於評估藥物使用安全性、藥物不良反應監測、及擬定風險管理機制，因此 ISPE 成為此領域研究方法、藥物政策、及相關教育等議題討論之重要平台。本次會議，指導的學生可以入選壁報發表，向其他研究者說明自己的研究成果並互相討論，並解釋台灣健保資料庫所涵蓋的內容，提升台灣研究在國際上曝光率，與會期間也有碰到在國外就學的台灣學生，他們未來都可成為國內的種子。

(四) 建議事項：

1. 國內衛生主管機關考慮有代表加入 ISPE，成為會員：

近年來歐美國家的衛生主管機關如 FDA、EMA 逐漸公告 RWE 做為決策參考的準則，可預期 RWE 的應用性會日益增加。我國健保資料庫是全球難得有單一涵蓋率高的資料庫，是台灣進行醫療相關研究如藥物安全性、風險評估等相當重要的研究資料來源，資料間有很強的連結性，可以長期追蹤，目前有許多學者利用健保資料庫為主要研究材料，也引起歐美國家許多研究者對我國資料庫的興趣，台灣雖然不會是第一個上市新藥使用的國家，但可以是有完整追蹤的資料來源，因此若可以建立合作管道進行多國研究,研究結果可提供國內衛生主管機關進行決策或臨床醫師治療參考，也可以提升台灣在國際上的知名度。

前陣子國內人民團體藉由釋憲，要在三年內提出健保資料庫合理使用的改善方案，有關保險資料的研究使用與個資安全等相關議題一直被熱烈討論，其他國家也面臨相同問題，雖然我國健保資料庫涵蓋率高，具有代表性，於研究的完整性有很大優勢，然而有關個資的利用範圍也不能被忽視。考慮此類研究皆為提昇國人用藥安全與治療品質，需要主管機關訂定合理的管理機制，讓研究得以在確保個資安全的前提下仍可以分析進行研究。

2. 建立我國 RWE 的法規及審查機制：

如何正確使用資料庫進行分析、解讀是一個重要議題，國內主管機關除了應考慮派員參與會議外，也建議可以參照歐美國家培育相關人才，用於審查 RWE 的結果，或是像美國 FDA 一樣以學術委託的方式，讓哈佛大學的學者審查，並且建立國家的準則。除了健保資料庫外，各醫療院所的就醫資料如電子病歷，統稱為 Electronic Medical Records (EMR)，也是一個重要的資料來源。這次在大會也有聽到許多國家討論 EMR 串連及可以補足投保

資料庫中所缺乏的實驗室檢查數值、抽煙、喝酒和生活習慣等變項。我國應該也可以考慮如何進行各醫院資料的串連，擴展研究領域及深度。但是同樣地，，如何在確保個資安全的前提下進行資料整合，需要國內更多專家學者與政府官員參與，以建立我國 RWE 的法規及審查機制。

3. 透過專業學會鼓勵參加亞洲區藥物流行病學年會：

2014年臺灣曾取得舉辦第三十屆的國際藥物流行病學年會，是第一次在歐美國家以外舉行年會，與會的國外學者皆對該會議的舉辦讚賞有加。今年，第十四屆亞洲藥物流行病學研討會將在台南舉辦，相較於ICPE的年度會議，此會議對我國相關的研究者來說，在參加的費用與交通負擔相對較少。由於疫情的關係，會議將於2022年10月21日至23日於臺南國立成功大學醫學院以複合式 (Hybrid) 的方式舉辦。會議邀請國內外知名的學者專家分享研究發展的新視野，建議國內主管機關人員、學者或研究人員可參加今年舉辦的亞洲藥物流行病學年會，增加交流溝通與增長見聞之機會。

附錄

壁報摘要

Dynamic pattern of anti-epileptic drug during pregnancy among women with epilepsy by using linking database in Taiwan.

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Background: Most studies indicated that birth rates in women with epilepsy (WWE) were lower than other groups and the modification of anti-epileptic drugs (AEDs) during pregnancy was also recommended. However, there are few reports about AEDs switching pattern between pre-conception and different trimesters.

Objective: This study aim was to evaluate the dynamic AEDs exposure pattern before and during pregnancy in women with epilepsy (WWE) by using linking database in Taiwan.

Method: We selected a cohort of women who aged from 15 to 55 yrs and ever diagnosed with epilepsy in 2009 to 2018. Pregnancy women with prenatal visit records were identified and the last menstrual period (LMP) was evaluated through linked data from Birth Certificate Database and Maternal and Child Health Database (MCHD), where were records of women with gestational week more than 20 weeks including still birth. The definition of pregnant women with active epilepsy was who at least two outpatient visits for epilepsy or at least one hospitalization of epilepsy within two years prior to conception. We performed Sankey diagrams to present the changes of AEDs utilization in pregnancy over time. IF mother with gestational age less than 24 weeks were excluded from the analysis for lacking of 3rd trimester. AEDs were classified to 1st and 2nd generation according to the time to market. Patient who exposed to both 1st and 2nd generation were classified as 2nd generation users and who exposed to at least two AEDs with different mechanism were classified as polytherapy.

Results: Around 7.4% (6,441/86,519) WWE achieved pregnant and 89% (5,712/6,441) have birth record. In the linked database, 93% of mothers' LMP date could be established. 2,027 WWE with active epilepsy were considered to be continuing their pharmacotherapy during pregnancy and 2,021 subjects were included

for analyzing. 42% of pregnant WWE didn't receive AEDs therapy before conception, and the proportion of un-exposure ones were increased accompanied with trimesters and decreased after delivery. In Sankey diagram, we found that 80% of exposure WWE didn't change the AED type and 50% to 70% un-exposed subjects changed to use 2nd generation AEDs when needed. Prescribing rate of 1st generation was decreased from 18% to 11%. For polytherapy users, the prescribing rate was declined from 34% to 27% during pregnancy and back to 31% after deliveries.

Conclusions: The dynamic pattern of AEDs in Taiwan was similar with Western countries. The outcome of maternal or neonatal still need to investigate in further study.

Drug Utilization Pattern of Non-Steroidal Anti-Inflammatory Drugs among Pre-End-Stage Renal Disease Patients in Taiwan

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Background: Due to high incidence and prevalence rates of end stage renal disease (ESRD), optimal care for pre-ESRD (chronic kidney disease stage 3b-5, CKD 3b-5) patients to delay progression to ESRD has become a priority in Taiwan. Non-steroidal anti-inflammatory drugs (NSAIDs) have been known as nephrotoxic drugs and guidelines suggest NSAIDs should be avoided or do not use for long-term duration in CKD patients. Appropriate use of NSAIDs to avoid preventable adverse events on the kidney needs more attention in pre-ESRD patients. However, limited studies have evaluated drug utilization pattern of NSAIDs in Taiwan pre-ESRD patients.
Objectives: To investigate the drug utilization pattern of NSAIDs in pre-ESRD patients who were enrolled in Taiwan pre-ESRD pay-for-performance program.
Methods: Data from Taiwan National Health Insurance Database, which enrolls about 99% of Taiwan's population of 23 million, was used to analyze the utilization pattern. Pre-ESRD patients who progressed to ESRD between 2012 and 2017 were included in the study. We excluded patients if they were younger than 20 years old, pregnant women or with medical history of malignancy. NSAIDs users were defined as patients who had at least one recorded prescription of NSAIDs within 1 year before they progressed to ESRD. We assessed patient characteristics between NSAIDs users and NSAIDs non-users which include patient demographics, comorbidities and co-medications. We performed multiple logistic regression models to estimate the risk factors. We further evaluated the utilization pattern of NSAIDs according to accreditation level, medical department, abnormal use of NSAIDs (which was defined as total days of NSAIDs prescribed within 3 months that is more than 30 days), and classification of NSAIDs.
Results: Total 32550 eligible patients were identified, and 17733 of whom were

NSAIDs users. According to accreditation level, primary clinics prescribed NSAIDs most frequently (62.7%). The most frequently prescribed medical department was division of family medicine (23.95%). 15.69% patients (2782 patients out of the 17733) used NSAIDs abnormally. By classification of NSAIDs, non-selective NSAIDs were prescribed most frequently (91.41%). Patients with upper respiratory tract infections and influenza [odds ratio (OR)=2.48, 95% confidence interval (CI)=2.37-2.61], osteoarthritis (OR=2.02, 95% CI=1.81-2.26) and fractures (OR=1.98, 95% CI=1.80-2.19) were more likely to increase use of NSAIDs. **Conclusions:** Many pre-ESRD patients still use NSAIDs abnormally. Intervention strategies including communicating the nephrotoxicity and interaction of NSAIDs to healthcare professionals as well as providing education for pre-ESRD patients to reduce NSAIDs use are needed.

Comparative safety of beta-blocker and calcium channel blockers in patients with chronic obstructive pulmonary disease and atrial fibrillation: a national population cohort study in Taiwan

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Background: Previous studies had established the benefits and safety of beta-blocker (BB) in chronic obstructive pulmonary disease (COPD)patients with myocardial infarction (MI) or congestive heart failure (CHF). However, safety of beta-blockers used in COPD patients with atrial fibrillation (AF) was still controversial. Objectives: To evaluate the real-world comparative risk of beta-blockers and non-dihydropyridine calcium channel blockers (CCB) for patients with COPD and AF.
Methods: We conducted a retrospective cohort study using the National Health Insurance Database from 2009-2018. Patients with prevalent COPD and incident AF were enrolled in this study. We divided patients into BB or CCB group based on the first prescription (the date was index date) after the first AF diagnosis and excluded patients received both BB and CCB. The primary outcome was all-cause mortality, and secondary outcome was emergency room visit or hospitalization due to COPD with acute exacerbation (COPDAE). We collected baseline characteristic 1-year before index date and presented as mean (standard deviation, SD) or number (percentage). We applied Kaplan-Meier method to estimate cumulative incidence rate and log-rank test to determine the difference. Finally, we used cox-proportional hazard model to calculate the hazard ratio (HR) and 95% confidence interval (CI).
Results: Total 41523 patients were enrolled in this study, 22598 in BB group (54.4%) and 18925 in CCB group (45.6%). We found 57.1% patients received selective BB in BB group. From baseline characteristic, the history of CHF, MI and ischemic heart disease (IHD) were respectively 43.2%, 7.9%, and 45.5% in BB group and 41.9%, 4.9% and 38.8% in CCB group. During 1 year before index date, 10.5% in BB group and 17% in CCB group had at least 1 episode of COPDAE, whereas 2.5% in BB group and 7.1% in CCB group occurred three times and above. After 1-year follow-up, the mortality was 23% in BB group and 34% in CCB group Log-rank test also showed significant difference for 2 groups in mortality and COPDAE. Finally, compared with CCB group, BB group was associated with a lower risk of mortality (adjusted HR=0.86; 95% CI 0.83-0.88) and lower risk of COPDAE (adjusted

HR=0.68; 95% CI 0.65-0.71). Moreover, we applied several subgroup analyses and found that either selective BB or non-selective BB had a lower risk of mortality and COPDAE. We also found that regardless of patient with CHF and MI or not, the risk was lower in BB group.

Conclusions: The use of BB in patients with COPD and AF associated with a lower risk of mortality and COPDAE compared with use of CCB. The association was independent of the selectivity of BB, presence or absence of CHF and MI. In further studies, subgroup analysis of severe COPD cases and other sensitivity analysis are needed.

The risk of serious infection in Crohn's disease patients treated with biologics: an external comparator cohort study

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Background: Although biologicals were reimbursed for Crohn's disease patients in Taiwan since 2011, serious infection during biological treatment is still controversial, because the indications for biologicals are narrow and not likely to be present in parallel comparison groups.
Objective: To evaluate the serious infection associated with biologicals in Crohn's disease (CD) using external comparation group.
Method: A retrospective cohort study was conducted using National Health Insurance data (NHID) from 2003- 2018. We compared CD patients on biological therapy in the post-biological era (POB, 2011-2018) with a historical control group as biologics-naïve CD patients in pre-biological era (PRB, 2003-2010). For the POB, the index date was the 1st biological prescription date. For PRB, the index date was randomly assigned by computer according to the duration between the 1st CD-related medication and 1st biologics date of the POB. Study outcome defined as mild infections (outpatients visit) and severe infection (emergency room visit, or hospitalization). To control the measurable confounding factors, inverse probability of treatment weighting (IPTW) estimation was applied. The hazard ratio (HR) and 95% confidence interval (CI) were calculated by cox regression with intention-to-treat (ITT) and as treated (AT) analysis.
Result: A total of 506 CD patients (PRB: 286; POB: 220) were included. The mean age was respectively 40 (14.5) years in PRB and 37.2 (14.2) years in POB. The baseline characteristics was similar between 2 eras. The cumulative probability of infections was no significantly increased during biologic use (logrank test, mild infection p=0.15, severe infection p=0.75). The incidence rate (per 1000 person-years) in mild infection was 1376 in POB, and 1701 in PRB and severe infection was 231 in POB, and 230 in PRB, respectively. After IPTW with ITT analysis, there was no increased risk in mild (HR, 0.85; 95% CI, 0.68-1.06) or sever (HR, 1.09; 95% CI,0.71-1.69) infection during biologics treatment period. We also had the same

finding with AT analysis. Stratification in the site of infection or restriction patients with previous conventional medication, there was no significant risk for mild or severe infection.

Conclusion: Compared to conventional therapy, biological therapy in CD patients does not increase infection risk. The result provided evidence in safety profile when selecting medications for CD patients.