高血壓疾病資料庫應用舉隅

-子資料庫在研究上的應用

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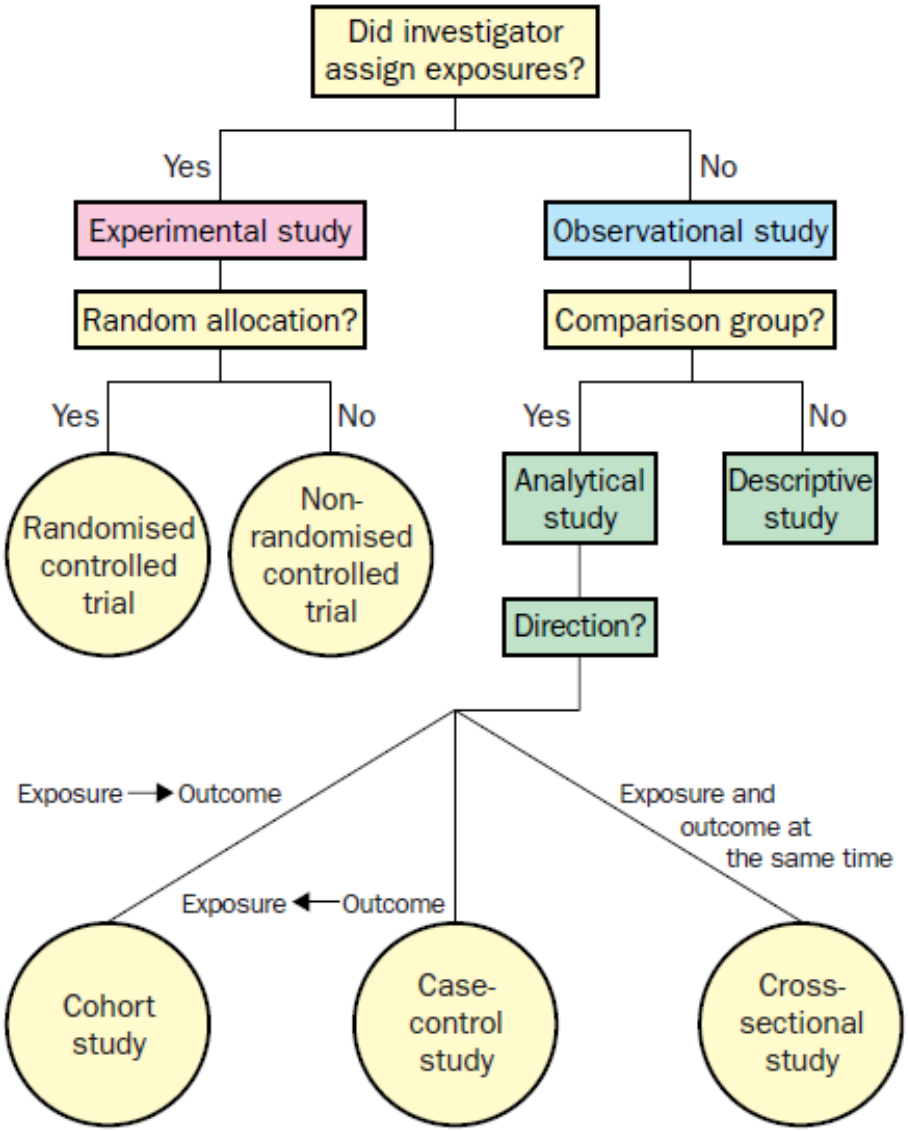
洪燕妮 台北醫學大學高齡健康管理學系 助理教授

研究者關心那些高血壓相關議題?

- 描述性統計
  - 發生率,盛行率, 死亡率?
  - 醫療利用與醫療費用?
  - 治療方法/用藥型態如何?
  - 年度趨勢?性別差異?年齡差異?區域差異?...
- 推論性統計
  - 那種治療比較好?
  - 那些族群/問題與高血壓相關 ?
    - 高血壓的病人發生那些問題的風險高?
    - 那些疾病的人發生高血壓的機率較高?

要採用那一種研究設計



Source: Grimes, D. A. and K. F. Schulz (2002), Lancet **359**

分析的單位(Unit of analysis)

- Patient as unit of observation
- Physician as unit of observation
- Hospital as unit of observation
- Region as unit of observation

照護品質的面向

- Structure indicators
  - 每萬人口醫師數
  - 每萬人口病床數
  - 受過特定訓練的人員數
- Process indicators:
  - 遵從疾病照護的指引的情形
  - Utilization of specific procedure
    - Use of ACEI and in Patients with Type 2 Diabetic CKD
    - Utilizing Preventive Health Service
    - Overstay in hospital
- Outcome indicators
  - Mortality(link Dataset of Death registration)
    - Inpatient mortality
    - 14 days mortality, 1 year mortality, 5 years mortality, etc.
    - Survival time
  - Hospital-acquired Infection
  - Unscheduled return ER (ICU or OR) within 24 (or 48, 72) hours
  - Unscheduled readmission
  - Complication of disease (or specific procedure)
    - Vascular access failure of Hemodialysis patient
    - Antipsychotic Drug Use and cardiovascular problems

主要影響因素/重要的自變項(Main effect)

- Compare different clinical status
  - Stage of cancer
  - DM vs non-DM
- Compare different treatment
  - drugs (ACEI , ARB)
  - modality(PD vs. HD, AVF vs. AVG, ringed vs non-ringed graft)
  - Operating type (白內障手術, 甲狀腺切除,子宮切除, 肺臟切除術等)
- Compare different provider's characteristics
  - Hospital level or physician level
  - Public vs. private hospital
  - scale of hospital (beds)
  - Different levels of volume

校正(控制)重要風險因子

- Find important risk factors from literature or professional opinions
- Defined these risk factors in claim data
  - 共病症(Comorbidity)
- Using proper method to adjust these factors
  - 傾向分數(Propensity score)

健保資料庫可以做那些主題的高血壓研究?

高血壓相關期刊論文-健保資料庫 (2008-2015)

- *Antihypertensive medication prescription patterns and time trends for newly-diagnosed uncomplicated hypertension patients in Taiwan.* BMC health services research, 2008.
- *Relationship of blood pressure control and hospitalization risk to medication adherence among patients with hypertension in Taiwan.* American journal of hypertension, 2010
- *Angiotensin II receptor blockers and risk of cancer in patients with systemic hypertension.* The American journal of cardiology, 2011.
- *Increased risk of hypertension in patients with major depressive disorder: a population-based study.* Journal of psychosomatic research, 2012..
- *Reverse epidemiology of hypertension-mortality associations in hemodialysis patients: a long-term population-based study.* American journal of hypertension, 2012.
- *Angiotensin-receptor blockers and risk of Alzheimer's disease in hypertension population.* Circulation Journal, 2013
- *Risk of insomnia attributable to β-blockers in elderly patients with newly diagnosed hypertension.* Drug metabolism and pharmacokinetics, 2013.
- *A predisposition for allergies predicts subsequent hypertension, dyslipidemia, and diabetes mellitus among patients with schizophrenia or bipolar disorder: A nationwide longitudinal study.* Schizophrenia research, 2014
- *Prescription pattern of Chinese herbal products for hypertension in Taiwan: A population-based study.* Journal of ethnopharmacology, 2014.
- *Increased risk of hypertension in patients with anxiety disorders: A population-based study.* Journal of psychosomatic research, 2014.
- *Synergistic effect of gestational hypertension and postpartum incident hypertension on cardiovascular health: A nationwide population study.* Journal of the American Heart Association, 2014.
- *Resistant hypertension, patient characteristics, and risk of stroke.* PLOS one, 2014
- *Risk of Systemic Hypertension and Cerebrovascular Accident in Patients With Aortic Coarctation Aged< 60 Years (from a National Database Study).* The American journal of cardiology, 2015.
- *Frequency and co-prescription pattern of Chinese herbal products for hypertension in Taiwan: a Cohort study.* BMC complementary and alternative medicine, 2015.
- *Different angiotensin-converting enzyme inhibitors and the associations with overall and cause-specific mortalities in patients with hypertension.* American journal of hypertension, 2015.
- *Association of Short-Term Use of Nonsteroidal Anti-Inflammatory Drugs With Stroke in Patients With Hypertension.* Stroke, 2015.

研究對象

- 高血壓病人
  - Incident case or prevalent case
  - 年齡限制 (>=20 y/o, >=65 y/o)
    - Chang, C.-H., et al., Different angiotensin-converting enzyme inhibitors and the associations with overall and cause-specific mortalities in patients with hypertension. American journal of hypertension, 2015. 28(6): p. 823-830.
    - Chang, C.-H., et al., Risk of insomnia attributable to β-blockers in elderly patients with newly diagnosed hypertension. Drug metabolism and pharmacokinetics, 2013. 28(1): p. 53-58.

- 其他疾病或狀況→ 發生hypertension的風險
  - Chen, M.-H., et al., *A predisposition for allergies predicts subsequent hypertension, dyslipidemia, and diabetes mellitus among patients with schizophrenia or bipolar disorder: A nationwide longitudinal study.* Schizophrenia research, 2014. **159**(1): p. 171-175.
  - Chien, C.-C., et al., *Reverse epidemiology of hypertension-mortality associations in hemodialysis patients: a long-term population-based study.* American journal of hypertension, 2012. **25**(8): p. 900-906.
  - Wu, E.-L., I.-C. Chien, and C.-H. Lin, *Increased risk of hypertension in patients with anxiety disorders: A population-based study.* Journal of psychosomatic research, 2014. **77**(6): p. 522-527.
  - 12. Wu, E.-L., et al., *Increased risk of hypertension in patients with major depressive disorder: a population-based study.* Journal of psychosomatic research, 2012. **73**(3): p. 169-174.

用藥情形

- Six major categories of antihypertensive drugs
  - Angiotensin-converting enzyme (ACE) inhibitors
  - Angiotensin receptor blockers (ARBs)
  - Beta-blockers
  - Calcium channel blockers (CCBs)
  - Diuretics
  - Others (all other antihypertensive classes including alpha-blockers)

- Dose
  - define daily dose
  - 連續使用: 若超過30天沒有用藥則稱為 discontinuation
  - The mean daily dose was estimated by multiplying cumulative number of pills dispensed by the dose prescribed and then divided by the follow-up duration. Data were presented in defined daily doses, the typical maintenance dose required

實例

- 描述性研究
  - Liu, P.-H. and J.-D. Wang, *Antihypertensive medication prescription patterns and time trends for newly-diagnosed uncomplicated hypertension patients in Taiwan*. BMC health services research, 2008. **8**(1): p. 133
- 推論性
  - Cohort study
  - Chang, C.-H., et al., ***Different angiotensin-converting enzyme inhibitors and the associations with overall and cause-specific mortalities in patients with hypertension***. American journal of hypertension, 2015. **28**(6): p. 823-830.
  - Case control study (case-crossover design)
    - Chuang, S.-Y., et al., *Association of Short-Term Use of Nonsteroidal Anti-Inflammatory Drugs With Stroke in Patients With Hypertension*. Stroke, 2015. **46**(4): p. 996-1003.

高血壓研究實例-描述性研究

- Liu, P.-H. and J.-D. Wang, *Antihypertensive medication prescription patterns and time trends for newly-diagnosed uncomplicated hypertension patients in Taiwan*. BMC health services research, 2008. **8**(1): p. 133.[Impact factor:1.68]
- **Background:** Knowledge of existing prescription patterns in the treatment of newly-diagnosed hypertension can provide useful information for improving clinical practice in this field. The aims of this study are to determine the prescription patterns and time trends for antihypertensive medication in newly-diagnosed cases of uncomplicated hypertension in Taiwan and to compare these with current clinical guidelines

Guidelines

- Based on clinical evidence and cost-effectiveness, guidelines developed by the Joint National Committee (JNC) in the United States and the National Institute for Health and Clinical Excellence (NICE) in the United Kingdom recommended that diuretics (particularly thiazide-type diuretics) should be the drug of first choice for patients with no compelling indications.

Methods-*Study population*

- This study uses a 200,000-person representative random sample from the computerized reimbursement database of the NHI, between January 1997 and December 2004.
- Details on the gender and date of birth of the patients, the date of prescription, commercial names of drugs, drug dosages/duration and costs for each prescription are recorded in the reimbursement files.
- Patients initially identified were newly-diagnosed with essential hypertension on at least three occasions, were being treated for this condition, and had received their first antihypertensive medication between 1 January 1998 and 31 December 2004. In order to verify that a case was a new one, a period of at least one year was required (January to December of 1997) without any treatment and/or diagnosis relating to hypertension.

- 排除共病症的干擾
  - diabetes mellitus, ischemic heart disease, diseases of pulmonary circulation, other forms of heart diseases (including dysrhythmia and heart failure), stroke or renal diseases were excluded from the sample.
  - any of the above diagnoses may not have appeared in any hospitalization file prior to the patient having been diagnosed as hypertensive, and the diagnoses may not have appeared more than three times in ambulatory outpatient files.

Prescription patterns of new cases of hypertension

- All antihypertensive drug prescription records from ambulatory care claims and prescriptions dispensed at contracted pharmacies were retrieved and analyzed for our sample of newly-diagnosed patients aged ≥30 years.
- Patients were stratified by gender and age, with age being split into two sub-groups: the younger group (30–54 years of age) and the older group (≥55 years).
- The clinical facilities were classified into four types, medical centers, regional hospitals, local hospitals and primary care clinics, based upon the level of medical care provided and the size of the institution as recognized by the NHI.

Antihypertensive drugs

- categorized according to the 1999 World Health Organization-International Society Hypertension Guidelines for the Management of Hypertension (WHO/ISH, 1999) and the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7)
- Six major categories of antihypertensive drugs
  - angiotensin-converting enzyme (ACE) inhibitors
  - angiotensin receptor blockers (ARBs)
  - beta-blockers
  - calcium channel blockers (CCBs)
  - Diuretics
  - others (all other antihypertensive classes including alpha-blockers).

- Prescriptions for a chronic disease in Taiwan, such as hypertension, most frequently involved the prescribing of drugs for 28- to 90-day periods(連續處方箋) which would allow the patient visit a doctor every one to three months.
- Since each prescription may have contained different combinations of drugs and durations of medication, analysis of the data was undertaken using the prescription rate as calculated as the number of prescriptions containing a specific antihypertensive agent divided by the total number of prescriptions.
- A comparison of the prescription time trend was undertaken for each year, beginning with the first antihypertensive prescription.
- Daily drug costs, excluding all pharmacy service fees or other peripheral costs, were also calculated for each prescription. The drug costs are set by the Bureau of NHI and universally applied to clinical facilities regardless of their sizes.

Statistical analysis

- After being weighted by duration of medication, daily drug costs are expressed as time-weighted means, while other results are expressed as means ± standard deviation (SD).
- The Chi-square test was carried out to determine the statistical significance of the differences between the prescription rates, with the Cochran-Armitage test also performed to assess the linear time trends over the sample period from the time of the initial treatment.
- Means of daily drug costs were compared using the Student t-test.
- multiple logistic regression analysis was performed to identify possible influential factors as a result of the prescribing of a single class of antihypertensive medication as a mono-therapy.
- SAS version 9.1 for Windows was used

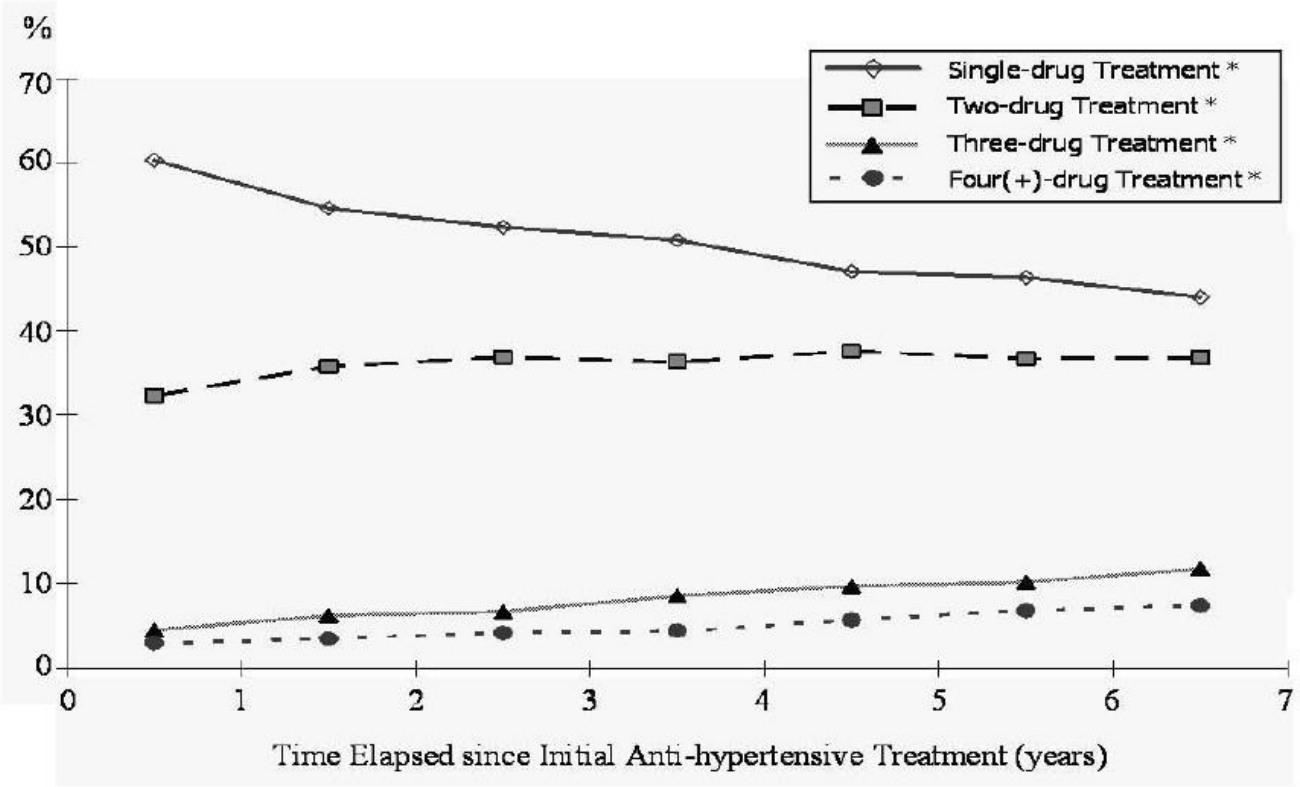


Figure 1
Prescription pattern time trends for combinations of mono-, two-, three- and four(+)-drug treatment therapies. Note: * indicates p-value <0.0125 under the Cochran-Armitage trend test, being significant with Bonferroni adjustment for multiple comparisons ($p < 0.05/4 = 0.0125$).

Table 1: Prescription patterns of antihypertensive therapies for newly-diagnosed uncomplicated hypertension patients, 1998–2004[a]

Variables	Treatment regimen								Total No. of prescriptions[c]
	Mono-therapy[b]		Two-drug combinations[b]		Three-drug combinations[b]		Four(+)-drug combinations[b]		
	No.	%	No.	%	No.	%	No.	%	
Patient gender									
Male	44 738	51.36#	31 494	36.16#	6 815	7.82#	4 058	4.66#	87 105
Female	50 059	54.62	31 927	34.84	6 024	6.57	3 639	3.97	91 649
Patient age (years)									
<55	40 357	50.67#	29 784	37.39#	6 130	7.70#	3 380	4.24	79 651
≥55	54 440	54.93	33 637	33.94	6 709	6.77	4 317	4.36	99 103
Type of clinical facility[d]									
Medical center	16 721	48.76#	12 693	37.02	3 897	11.37#	978	2.85#	34 289
Regional hospital	14 809	49.75#	10 453	35.11#	3 687	12.39#	819	2.75#	29 768
Local hospital	18 258	59.03#	9 745	31.51#	2 395	7.74#	531	1.72#	30 929
Primary care clinic	44 997	53.73	30 520	36.44	2 860	3.42	5 369	6.41	83 746
Total Nos.	94 797	53.03	63 421	35.48	12 839	7.18	7 697	4.31	178 754

Notes:
[a] Total sample number = 6 536 patients.
[b] No. refers to the number of prescriptions under each treatment regimen; % refers to the percentage of the total drugs prescribed under the four treatment regimens.
[c] As a result of missing data, the sum of the total number of prescriptions over the four types of clinical facilities is smaller than the overall number of prescriptions.
[d] Pairwise group comparisons are performed taking primary care clinics as the reference.
Significant p-value with the Bonferroni-adjusted α-level, $p < 0.0025$

Table 2: Distribution of antihypertensive drugs for newly-diagnosed uncomplicated hypertension patients, by gender, age and clinical facility, 1998–2004a

Variables	Class of drug[b]										Total No. of prescriptions[b]
	Diuretics		2 Beta-blockers		1 CCBs[c]		3 ACE inhibitors[c]		ARBs[c]		Others		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Patient gender													
Male	15 525	17.82#	34 703	39.84#	46 468	53.35#	22 825	26.20#	10 635	12.21#	15 212	17.46#	87 105
Female	19 981	21.80	40 941	44.67	46 106	50.31	21 306	23.25	10 339	11.28	8 826	9.63	91 649
Patient age (years)													
<55	13 556	17.02#	39 445	49.52#	40 270	50.56#	21 282	26.72#	10 421	13.08#	7 578	9.5#	79 651
≥55	21 950	22.15	36 199	36.53	52 304	52.78	22 849	23.06	10 553	10.65	16 460	16.61	99 103
Type of clinical facility[d]													
Medical center	7 729	22.54#	14 463	42.18#	18 675	54.46#	6 169	17.99#	7 764	22.64#	3 122	9.10#	34 289
Regional hospital	6 025	20.24	12 320	41.39#	17 058	57.30#	6 170	20.73#	5 637	18.94#	2 958	9.94#	29 768
Local hospital	5 005	16.18#	11 303	36.54#	17 849	57.71#	5 464	17.67#	3 594	11.62#	3 905	12.63#	30 929
Primary care clinic	16 745	19.99	37 540	44.83	38 988	46.56	26 322	31.43	3 966	4.74	14 053	16.78	83 746
Total Nos.	35 506	19.86	75 644	42.32	92 574	51.79	44 131	24.69	20 974	11.73	24 038	13.45	178 754

Notes:
[a] Total sample number = 6 536 patients.
[b] No. refers to the number of prescriptions for each class of drug; % refers to the percentage of the total prescriptions for the six classes of drugs. As a result of missing data, the sum of the total number of prescriptions over the four types of clinical facilities is smaller than the overall number of prescriptions. The sum of the prescription rates for all six classes of drugs exceeds 100% because the average prescription contained more than one drug.
[c] CCBs = calcium channel blockers; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers.
[d] Pairwise group comparisons are performed taking primary care clinics as the reference.
Significant p-value with the Bonferroni-adjusted α-level, $p < 0.0017$

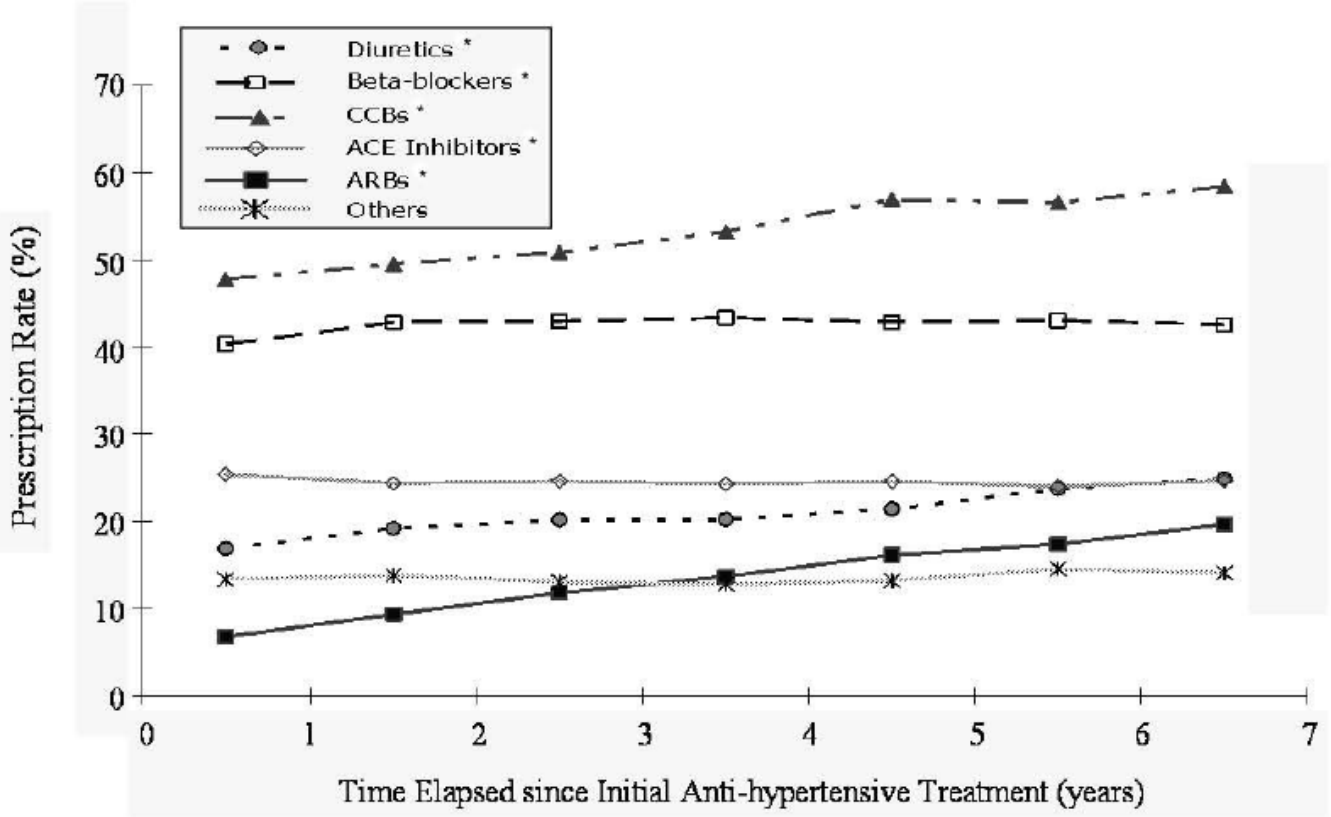


Figure 2
Prescription distribution time trends for antihypertensive agents. Note: * indicates p-value <0.0083 under the Cochran-Armitage trend test, being significant with Bonferroni adjustment for multiple comparisons ($p < 0.05/6 = 0.0083$).

Table 3: Distribution of mono-therapy antihypertensive drug prescriptions for newly-diagnosed uncomplicated hypertension patients[a]

Variables	Class of drug[b]										Total No. of prescriptions[b]
	Diuretics		Beta-blockers		CCBs[c]		ACE inhibitors[c]		ARBs[c]		Others		
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	
Patient gender													
Male	2 974	6.65#	11 602	25.93#	14 881	33.26	7 004	15.66	2 561	5.72	5 716	12.78#	44 738
Female	4 849	9.69	14 233	28.43	16 830	33.62	7 619	15.22	2 822	5.64	3 706	7.40	50 059
Patient age (years)													
<55	2 366	5.86#	13 627	33.77#	12 083	29.94#	7 134	17.68#	2 677	6.63#	2 470	6.12#	40 357
≥55	5 457	10.02	12 208	22.42	19 628	36.05	7 489	13.76	2 706	4.97	6 952	12.77	54 440
Type of clinical facility[d]													
Medical center	1 067	6.38#	4 474	26.76#	5 841	34.93#	2 255	13.49#	2 099	12.55#	985	5.89#	16 721
Regional hospital	1 026	6.93#	4 144	27.98	5 690	38.42#	1 710	11.55#	1 272	8.59#	967	6.53#	14 809
Local hospital	1 363	7.47#	4 171	22.84#	8 186	44.84#	1 728	9.46#	920	5.04#	1 890	10.35#	18 258
Primary care clinic	4 367	9.71	13 043	28.99	11 991	26.65	8 927	19.84	1 089	2.42	5 580	12.40	44 997
Total Nos.	7 823	8.25	25 835	27.25	31 711	33.45	14 623	15.43	5 383	5.68	9 422	9.94	94 797

Notes:
[a] Total sample number of prescriptions = 94 797.
[b] No. refers to the number of prescriptions for each class of drug; % refers to the percentage of the total prescriptions for the six classes of drugs. As a result of missing data, the sum of the total number of prescriptions over the four types of clinical facilities is smaller than the overall number of prescriptions.
[c] CCBs = calcium channel blockers; ACE = angiotensin-converting enzyme; ARBs = angiotensin receptor blockers.
[d] Pairwise group comparisons are performed taking primary care clinics as the reference.
Significant p-value with the Bonferroni-adjusted α-level, $p < 0.0017$

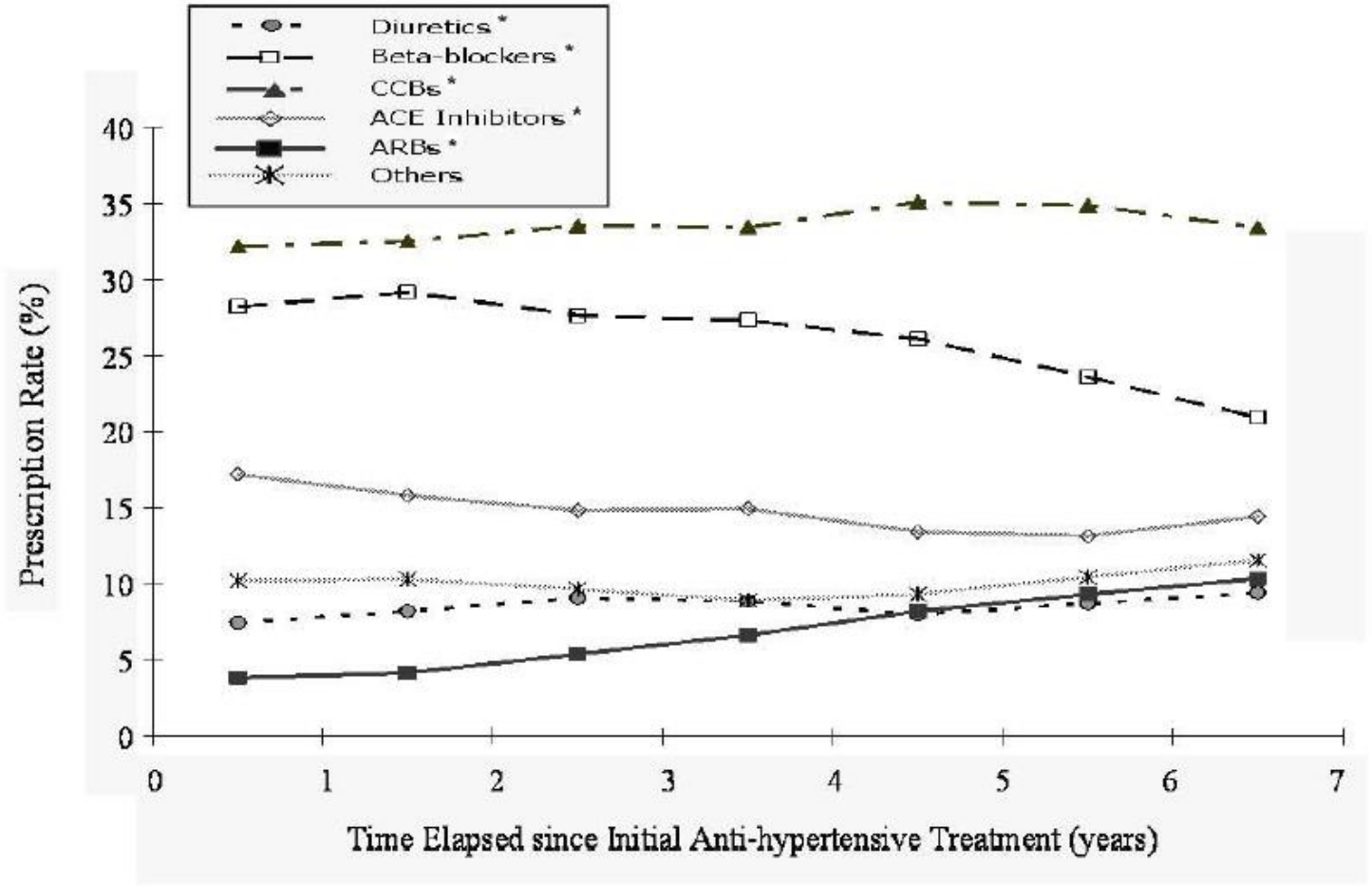


Figure 3
Time trends for single-drug antihypertensive treatment. Note: * indicates p-value <0.0083 under the Cochran-Armitage trend test, being significant with Bonferroni adjustment for multiple comparisons ($p < 0.05/6 = 0.0083$).

Table 4: Multiple logistic regression estimates of ARB and ACE inhibitor mono-therapy prescription characteristics for newly-diagnosed uncomplicated hypertension patients, 1998–2004*

Variables	ARBs		ACE inhibitors	
	OR	95% CI	OR	95% CI
Patient gender				
Female (reference)	1.00	-	1.00	-
Male	0.99	0.94–1.05	1.07	1.03–1.11
Patient age (years)				
30–54 (reference)	1.00	-	1.00	-
≥55	0.74	0.70–0.78	0.75	0.72–0.78
Geographical region				
Northwest (reference)	1.00	-	1.00	-
Midwest	0.74	0.68–0.80	0.98	0.93–1.02
Southwest	0.67	0.62–0.72	0.86	0.82–0.90
Eastern	1.34	1.19–1.52	1.39	1.29–1.49
Offshore islands	2.78	2.21–3.49	0.45	0.35–0.57
Type of clinical facility				
Primary care clinics (reference)	1.00	-	1.00	-
Local hospitals	2.17	1.98–2.38	0.43	0.41–0.45
Regional hospitals	3.55	3.26–3.87	0.52	0.49–0.55
Medical centers	5.77	5.32–6.25	0.63	0.60–0.66
Time elapsed since initial therapy				
1 year or less (reference)	1.00	-	1.00	-
2–3 years	1.00	0.92–1.09	0.93	0.89–0.97
4–7 years	1.12	1.03–1.21	0.95	0.90–1.00
Comorbidity after hypertension†				
Diabetes mellitus	1.55	1.42–1.68	1.36	1.28–1.44
Ischemic heart disease	1.10	1.02–1.19	0.78	0.73–0.82
Stroke	1.02	0.93–1.11	0.98	0.91–1.05
Chronic renal disease	1.07	0.94–1.22	0.92	0.83–1.02
Calendar years				
1998–2000 (reference)	1.00	-	1.00	-
2001–2002	2.35	2.12–2.62	0.87	0.83–0.91
2003–2004	4.45	4.01–4.94	0.79	0.75–0.83

Notes:
* The odds ratio (OR) for each variable was adjusted for all other variables listed in the table.
† The reference group is subjects with no corresponding comorbidity for each category after hypertension.

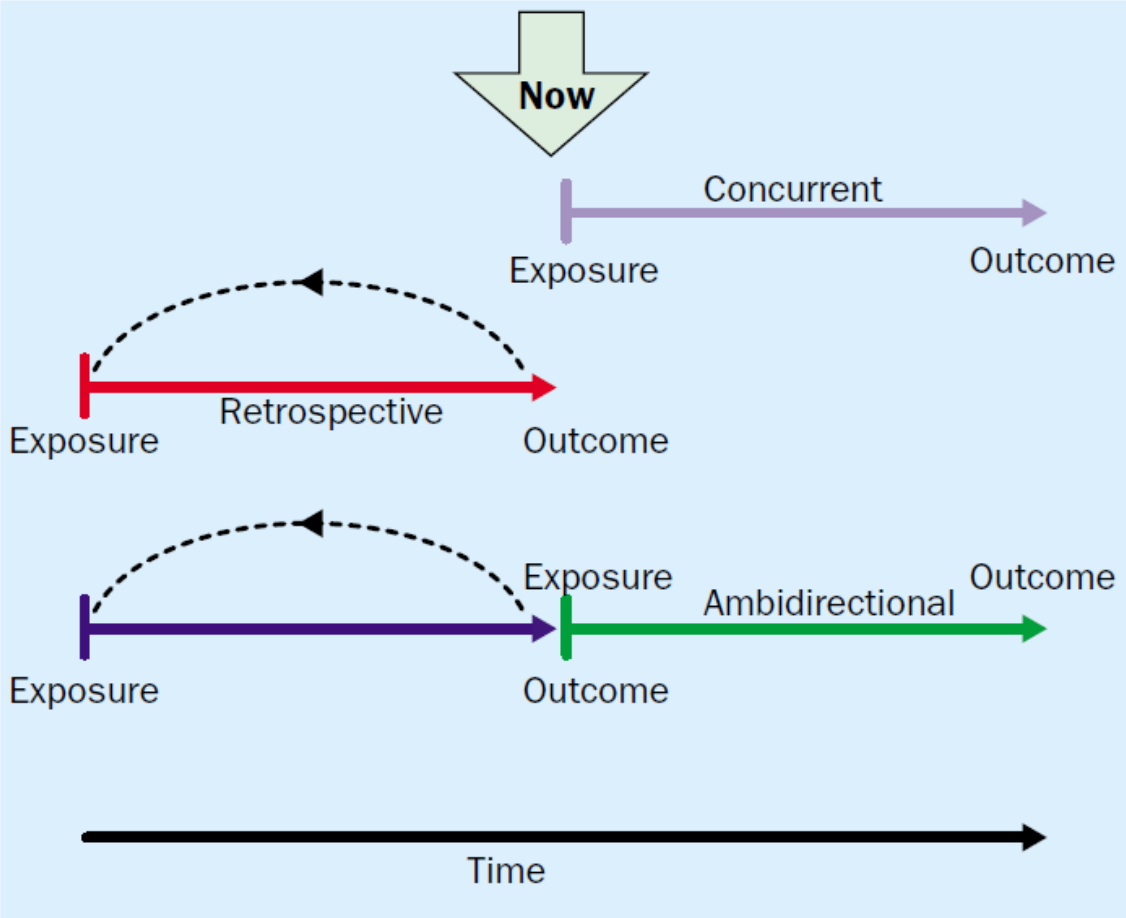
Conclusion

- The initial prescription patterns for antihypertensive therapies for uncomplicated hypertension in Taiwan seem to be inconsistent with the current international clinical guidelines.
- diuretics are the least expensive class of antihypertensive drugs, with a notably low prescription rate.
- growing trend in the prescribing of ARBs as the initial choice of therapy for uncomplicated hypertension, particularly in medical centers and regional hospitals.
  - need for greater awareness of the evidence-based guidelines for antihypertensive drug therapy amongst physicians and the general public.
- there is still significant room for improvement in the cost-effectiveness of antihypertensive treatment.
- recommend reaching a consensus on this matter and developing a domestic clinical guideline taking cost-effectiveness into consideration as soon as possible.

高血壓研究實例[2]-Cohort study

- Chang, C.-H., et al., ***Different angiotensin-converting enzyme inhibitors and the associations with overall and cause-specific mortalities in patients with hypertension***. American journal of hypertension, 2015. **28**(6): p. 823-830.[Impact factor: 2.852]
- **BACKGROUND**
  - Angiotensin-converting enzyme (ACE) inhibitors have been widely used in the treatment of hypertension, but the comparative effectiveness in reducing mortality among different drugs is seldom reported.
- **Hypothesis**
  - hypertensive patients treated with the reference therapy, ramipril, would demonstrate a lower associated risk of mortality compared with those treated with other ACE inhibitors.

Schematic diagram of concurrent, retrospective, and ambidirectional cohort studies



Source: Grimes, D. A. and K. F. Schulz (2002), Lancet **359**

METHODS-Data source

- The current analyses linked several large computerized claims datasets with the National Death Registry through the use of birth dates and civil identification numbers unique to each beneficiary.

Study population

- Patients aged more than 20 years who initiated **enalapril, captopril, lisinopril, fosinopril, perindopril, ramipril, or imidapril** between 1 January 2004 and 31 December 2009 were identified.
- Quinapril, benazepril, cilazapril, and trandolapril were excluded due to insufficient numbers.
- Initiation was defined as free of angiotensin receptor blockers or ACE inhibitor therapy for 12 months prior to the first prescription (index date).
- Exclude criteria
  - 100 years of age or older
  - Without continuous insurance coverage for 12 months before the index date
  - Treated with multiple ACE inhibitors on the index date
  - Without prior diagnosis of hypertension in the inpatient and outpatient database
  - Diagnosed with cancer prior to the index date.

Use of study drugs

- The mean daily dose=
  - (cumulative number of pills dispensed)X(dose prescribed)/(follow-up duration)
- Defined daily doses (DDD): the typical maintenance dose required when the drug is used for its main indication in an adult

Medication	ATC codes (Anatomical Therapeutic Chemical classification)
Angiotensin receptor blockers	C09CA01, C09CA03, C09CA04, C09CA06, C09CA07, C09CA08,
ACE inhibitors	C09AA
Captopril	C09AA01
Enalapril	C09AA02
Lisinopril	C09AA03
Fosinopril	C09AA09
Perindopril	C09AA04
Ramipril	C09AA05
Imidapril	C09AA16
Alpha-blockers	C02CA
Beta-blockers	C07A
Calcium channel blockers	C08
Diuretics	C03
Other anti-hypertensive agents	C02A, C02B, C02CC, C02D,

第一碼 解剖位置
C: CARDIOVASCULAR SYSTEM

Covariate ascertainment and adjustment

- Inpatient and outpatient diagnosis files and prescription files during the 12-month period before the index date were used to ascertain
  - Patients' medical history
  - Demographic data
  - Medication use (anatomical therapeutic chemical codes)
  - Resource utilization
  - Monthly income was used as a proxy of socioeconomic status.

Outcome ascertainment

- Primary outcome: overall mortality
  - The vital status and date of death for the study participants were ascertained by linkage to the National Death Registry using each subject's unique identification number.
- Secondary outcome: Cause of death (ICD-9, ICD-10)
  - Cardiovascular
  - Cerebrovascular
  - Cancer

Statistical analysis[1]

- Baseline characteristics were summarized and person–days of follow-up were computed for each ACE inhibitor category.
- The crude overall and cause-specific mortality rates were calculated and their 95% confidence intervals (CIs) were estimated based on a Poisson distribution.
- All ACE inhibitor users were followed within their initiation groups (the intention-to-treat analysis) until the study end as determined by last outpatient visit or hospitalization before 31 December 2010 disregarding any changes in treatment status over time.
- A Cox proportional hazards regression model was used to calculate the hazard ratios (HR) and 95% CIs using ramipril as the common reference group.
- Separate models were further conducted to estimate the HRs of death due to cardiovascular disease, cerebrovascular disease, and cancer, and competing risk in between was modeled by cumulative incidence function.
-

Statistical analysis[2]

- Auxiliary analyses

  (i) controlling for a binary covariate for mean daily dosage (≥0.5 or <0.5 defined daily dose/day) estimated from the first ACE inhibitor prescription

  (ii) using a different follow-up protocol that censoring patients at the point of treatment switching or discontinuation (as-treated analysis)

  (iii) comparing exclusive users who remained on the initial treatment

  (iv) restricting to those participants who were followed for more than 1 year to see if the results changed substantially.

Statistical analysis[3]

- Stratified analyses were performed to evaluate potential effect modification.
  - (i) age (<70, ≥70 years)
  - (ii) diabetes
  - (iii) congestive heart failure
  - (iv) myocardial infarction
  - (v) stroke
  - (vii) chronic renal disease

Figure 1. Study flow

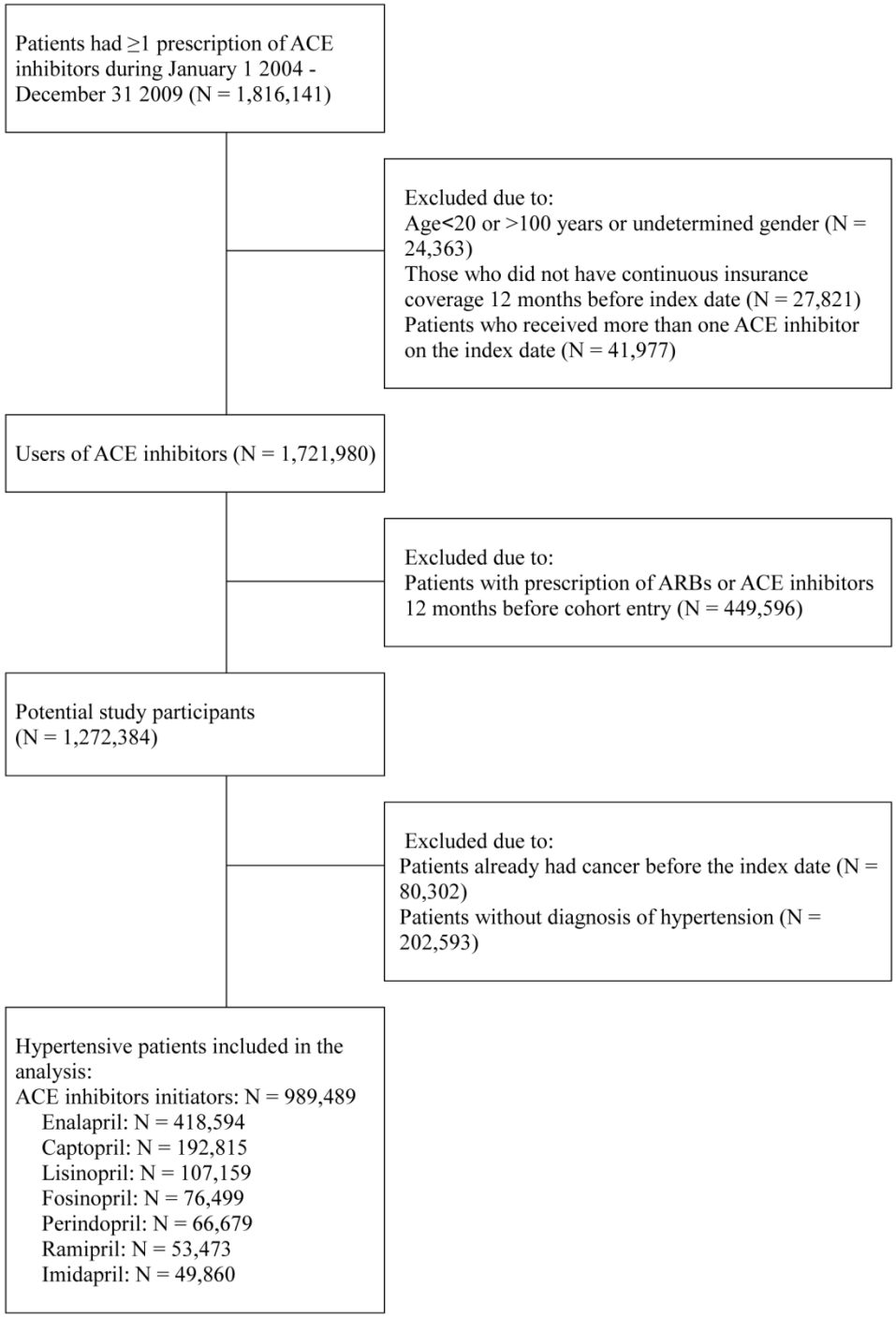


Table 1. Baseline characteristics, person–days, and crude overall and cause-specific mortality rates among initiators of ACE inhibitors

	Enalapril	Captopril	Lisinopril	Fosinopril	Perindopril	Ramipril	Imidapril
Drug information							
Defined daily dose	5 mg	50 mg	10 mg	10 mg	4 mg	2.5 mg	5 mg
Dosing frequency	QD	QD, BID, TID	QD	QD	QD	QD	QD
Tissue half-life	11 h	2 h	13 h	4 h	9 h	17 h	Imidapril 1.7 h Imidapril at 14.8 h
N	418,594	192,815	107,159	76,499	66,679	53,473	49,860
Patient characteristics							
Age at ARBs or ACE inhibitors initiation (mean ± SD)	58.91 ± 13.54	62.86 ± 14.38	58.95 ± 13.58	59.97 ± 13.76	60.18 ± 14.05	61.33 ± 14.12	60.19 ± 13.95
Male (%)	49.69	48.41	52.87	52.51	54.11	54.24	53.57
Exposed person–days	686,128,178	290,473,678	149,529,103	112,884,759	90,080,431	75,789,348	64,083,594
Mean follow-up years	4.49	4.12	3.82	4.04	3.70	3.88	3.52
Mean daily dosage (DDD)	0.43	0.27	0.38	0.33	0.42	0.60	0.34
Number of death	37,255	34,216	8,353	8,307	6,690	6,016	3,895
Crude overall mortality rate per 1,000,000 person–days (95% CI)	54.30 (53.75–54.85)	117.79 (116.55–119.04)	55.86 (54.66–57.06)	73.59 (72.01–75.17)	74.27 (72.49–76.05)	79.38 (77.37–81.38)	60.78 (58.87–62.69)
Number of cardiovascular death	5,613	5,954	1,294	1,260	1,118	1,047	689
Crude cardiovascular mortality rate per 1,000,000 person–days (95% CI)	8.18 (7.97–8.39)	20.50 (19.98–21.02)	8.65 (8.18–9.13)	11.16 (10.55–11.78)	12.41 (11.68–13.14)	13.81 (12.98–14.65)	10.75 (9.95–11.55)
Number of cerebrovascular death	4,058	4,413	948	955	903	759	441
Crude cerebrovascular mortality rate per 1,000,000 person–days (95% CI)	5.91 (5.73–6.10)	15.19 (14.74–15.64)	6.34 (5.94–6.74)	8.46 (7.92–9.00)	10.02 (9.37–10.68)	10.01 (9.30–10.73)	6.88 (6.24–7.52)
Number of cancer death	7,759	4,372	1,671	1,364	1,035	907	657
Crude cancer mortality rate per 1,000,000 person–days (95% CI)	11.31 (11.06–11.56)	15.05 (14.61–15.50)	11.18 (10.64–11.71)	12.08 (11.44–12.72)	11.49 (10.79–12.19)	11.97 (11.19–12.75)	10.25 (9.47–11.04)

Abbreviations: ACE, angiotensin-converting enzyme; ARBS, angiotensin receptor blockers; CI, confidence interval; DDD, defined daily dose.

Table 2. Hazard ratio of overall mortality and cause-specific mortality comparing individual ACE inhibitors with Ramipril

	Enalapril	Captopril	Lisinopril	Fosinopril	Perindopril	Imidapril
Overall mortality						
Crude	0.682 (0.664–0.701)	1.478 (1.438–1.519)	0.706 (0.683–0.729)	0.928 (0.898–0.960)	0.932 (0.900–0.965)	0.770 (0.740–0.802)
Adjusted	1.083 (1.052–1.114)	1.276 (1.241–1.313)	1.018 (0.985–1.053)	1.084 (1.048–1.120)	1.003 (0.969–1.039)	0.966 (0.928–1.007)
Cardiovascular mortality						
Crude	0.589 (0.552–0.630)	1.473 (1.379–1.572)	0.629 (0.580–0.682)	0.809 (0.746–0.878)	0.893 (0.820–0.971)	0.785 (0.713–0.864)
Adjusted	1.114 (1.039–1.195)	1.316 (1.231–1.408)	1.033 (0.951–1.123)	1.072 (0.987–1.165)	1.048 (0.963–1.141)	1.016 (0.921–1.120)
Competing risk analysis[a]	1.114 (1.038–1.196)	1.316 (1.229–1.410)	1.033 (0.950–1.123)	1.072 (0.986–1.166)	1.048 (0.962–1.142)	1.016 (0.920–1.121)
Cerebrovascular mortality						
Crude	0.601 (0.556–0.649)	1.532 (1.418–1.654)	0.631 (0.574–0.695)	0.849 (0.772–0.934)	0.995 (0.904–1.096)	0.678 (0.603–0.763)
Adjusted	1.017 (0.937–1.104)	1.269 (1.173–1.373)	0.991 (0.899–1.092)	0.998 (0.906–1.098)	0.966 (0.877–1.064)	0.909 (0.807–1.024)
Competing risk analysis[b]	1.017 (0.936–1.105)	1.269 (1.171–1.375)	0.991 (0.898–1.093)	0.998 (0.905–1.099)	0.966 (0.876–1.066)	0.909 (0.806–1.024)
Cancer mortality						
Crude	0.916 (0.855–0.981)	1.230 (1.145–1.321)	0.943 (0.870–1.022)	1.004 (0.924–1.092)	0.964 (0.882–1.054)	0.886 (0.801–0.979)
Adjusted	1.088 (1.013–1.168)	1.149 (1.068–1.236)	1.072 (0.987–1.163)	1.099 (1.011–1.196)	0.994 (0.909–1.086)	0.985 (0.891–1.090)
Competing risk analysis[c]	1.088 (1.013–1.168)	1.149 (1.068–1.237)	1.072 (0.987–1.163)	1.099 (1.010–1.196)	0.994 (0.909–1.087)	0.985 (0.891–1.090)

See Supplementary Table S2 for covariates included in the multivariable regression models.
[a]Cerebrovascular and cancer mortality as a competing risk.
[b]Cardiovascular and cancer mortality as a competing risk.
[c]Cardiovascular and cerebrovascular mortality as a competing risk.

Table 3. Auxiliary analysis of overall mortality comparing individual ACE inhibitors with ramipril

Sensitivity analysis	Enalapril	Captopril	Lisinopril	Fosinopril	Perindopril	Imidapril
Intention-to-treat approach						
Adjusted for baseline covariates	1.08 (1.05–1.11)	1.28 (1.24–1.31)	1.02 (0.98–1.05)	1.08 (1.05–1.12)	1.00 (0.97–1.04)	0.97 (0.93–1.01)
Adjusted for baseline covariates and mean daily dosage[a]	1.06 (1.03–1.10)	1.21 (1.17–1.24)	1.01 (0.98–1.04)	1.03 (1.00–1.07)	1.00 (0.97–1.04)	0.94 (0.90–0.98)
As-treated approach						
Crude	0.29 (0.25–0.33)	3.86 (3.43–4.34)	0.30 (0.25–0.36)	0.64 (0.54–0.75)	0.54 (0.46–0.65)	0.39 (0.32–0.49)
Adjusted	0.88 (0.77–1.02)	2.06 (1.83–2.32)	0.81 (0.68–0.97)	0.94 (0.80–1.11)	0.79 (0.66–0.94)	0.69 (0.55–0.85)
Restrict to exclusive users						
Crude	0.59 (0.57–0.62)	1.65 (1.59–1.72)	0.60 (0.57–0.63)	0.90 (0.85–0.94)	0.81 (0.77–0.86)	0.66 (0.62–0.70)
Adjusted	1.05 (1.00–1.09)	1.34 (1.28–1.39)	1.03 (0.98–1.09)	1.13 (1.07–1.19)	1.00 (0.94–1.05)	0.95 (0.90–1.01)
Restricting to those followed for more than 1 year						
Crude	0.74 (0.72–0.77)	1.33 (1.28–1.37)	0.79 (0.76–0.82)	0.96 (0.93–1.00)	1.00 (0.96–1.04)	0.84 (0.80–0.88)
Adjusted	1.08 (1.04–1.11)	1.20 (1.16–1.24)	1.03 (0.99–1.07)	1.09 (1.05–1.13)	1.02 (0.98–1.06)	0.99 (0.94–1.04)

Abbreviation: ACE, angiotensin-converting enzyme.
[a]Defined by the first ACE inhibitor prescription.

Table 4. Subgroup analyses: adjusted hazard ratios of overall mortality comparing individual ACE inhibitors with ramipril

	Enalapril	Captopril	Lisinopril	Fosinopril	Perindopril	Imidapril
Age						
< 70 years	1.12 (1.06–1.18)	1.33 (1.26–1.40)	1.09 (1.03–1.16)	1.08 (1.01–1.15)	1.05 (0.99–1.12)	0.94 (0.87–1.02)
≥ 70 years	1.06 (1.02–1.10)	1.22 (1.19–1.27)	0.98 (0.94–1.02)	1.08 (1.03–1.12)	0.98 (0.94–1.02)	0.97 (0.93–1.02)
Diabetes						
Yes	1.12 (1.07–1.18)	1.32 (1.26–1.38)	1.06 (1.00–1.12)	1.12 (1.06–1.18)	1.03 (0.97–1.09)	0.97 (0.91–1.04)
No	1.06 (1.03–1.10)	1.25 (1.20–1.29)	0.99 (0.95–1.04)	1.06 (1.01–1.10)	0.99 (0.94–1.03)	0.96 (0.91–1.01)
Congestive heart failure						
Yes	0.99 (0.93–1.06)	1.20 (1.13–1.27)	0.92 (0.84–1.00)	1.03 (0.95–1.11)	0.93 (0.86–1.01)	0.94 (0.86–1.04)
No	1.10 (1.07–1.14)	1.29 (1.25–1.33)	1.05 (1.01–1.09)	1.11 (1.07–1.15)	1.03 (0.99–1.07)	0.99 (0.94–1.03)
Myocardial infarction						
Yes	1.05 (0.91–1.20)	1.24 (1.11–1.38)	1.18 (0.97–1.44)	1.03 (0.87–1.22)	1.02 (0.87–1.20)	1.13 (0.92–1.40)
No	1.09 (1.05–1.12)	1.28 (1.24–1.32)	1.02 (0.98–1.06)	1.09 (1.05–1.13)	1.00 (0.97–1.04)	0.96 (0.92–1.01)
Stroke						
Yes	1.09 (1.02–1.16)	1.29 (1.22–1.37)	1.04 (0.96–1.12)	1.06 (0.99–1.14)	0.98 (0.92–1.06)	0.96 (0.87–1.05)
No	1.08 (1.05–1.12)	1.27 (1.23–1.31)	1.02 (0.98–1.06)	1.09 (1.05–1.13)	1.02 (0.97–1.06)	0.97 (0.92–1.01)
Chronic renal disease						
Yes	0.96 (0.86–1.06)	1.19 (1.08–1.30)	0.88 (0.78–1.00)	1.01 (0.91–1.12)	0.95 (0.84–1.07)	0.81 (0.69–0.95)
No	1.09 (1.06–1.13)	1.28 (1.24–1.32)	1.03 (1.00–1.07)	1.09 (1.05–1.12)	1.01 (0.98–1.05)	0.98 (0.94–1.02)

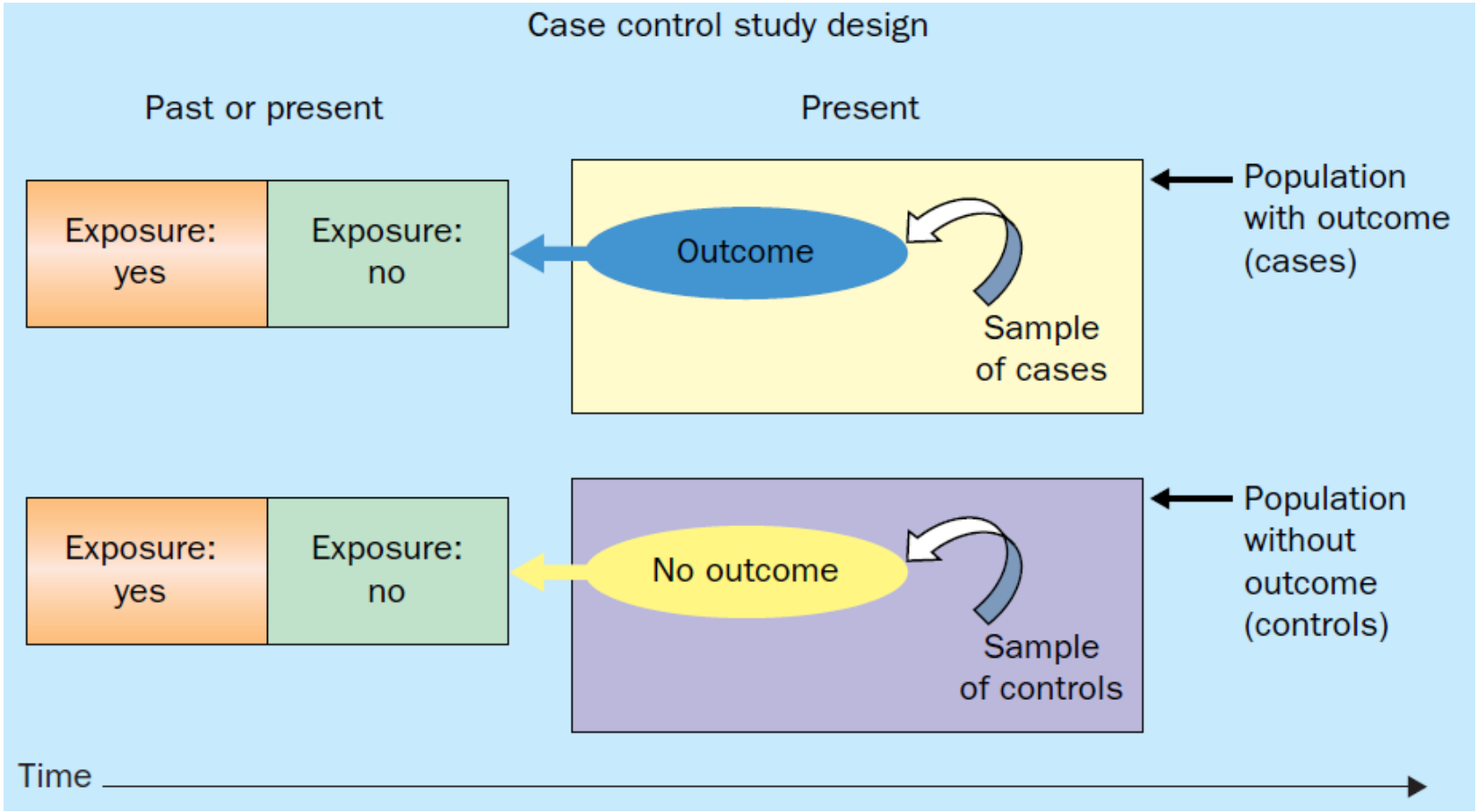
Abbreviation: ACE, angiotensin-converting enzyme.

Subgroup analyses:

高血壓研究實例3-Case-crossover study

- Chuang, S.-Y., et al., *Association of Short-Term Use of Nonsteroidal Anti-Inflammatory Drugs With Stroke in Patients With Hypertension*. Stroke, 2015. **46**(4): p. 996-1003.
- Impact factor: 5.723
- ***Background and Purpose***—Limited studies have investigated the risk of cerebrovascular events associated with the use of nonsteroidal anti-inflammatory drugs (NSAIDs)[非類固醇消炎止痛藥] in subjects at high risk.
- Examined the short-term (defined as 30-day period) effect of selective and nonselective NSAIDs use on the risk of ischemic and hemorrhagic stroke in patients with hypertension.

Schematic diagram of case-control study design



Methods-Data Source

- National Health Insurance Research Database (NHIRD)
  - the Longitudinal Health Insurance Database for the year 2005 derived from the NHIRD of 2005
  - the Longitudinal Health Insurance Database for the year2010 derived from the NHIRD of 2010.

Study Subjects

- We first identified patients with an incident stroke in 2010 as those with a hospitalized record for a primary diagnosis of a stroke event under *International Classification of Diseases-Ninth Revision*-CM codes: 433.x, 434.x, and 436.x for ischemic stroke and 430 and 431 for hemorrhagic stroke.
- Index date: the date that the subjects were diagnosed as having a hospitalized medical record of a stroke.
- Among those, we furthermore defined the study subjects as patients with diagnosis of hypertension (*International Classification of Diseases-Ninth Revision*-CM codes: 401–404 from either 2 outpatient claims records or 1 inpatient claims record during 1 year before the index date) and with antihypertensive prescription records during 1 year before the index date.
- Exclusion criteria
  - Aged <20 years in 2010
  - Had a prior inpatient admission or outpatient visits for stroke in 2009
  - With concurrent diagnosis of trauma or acute myocardial infarction at the same hospitalization
  - Hospitalized for any reason 120 days before the index date
- Total of **1653 study subjects** with hypertension were identified

資料處理流程圖

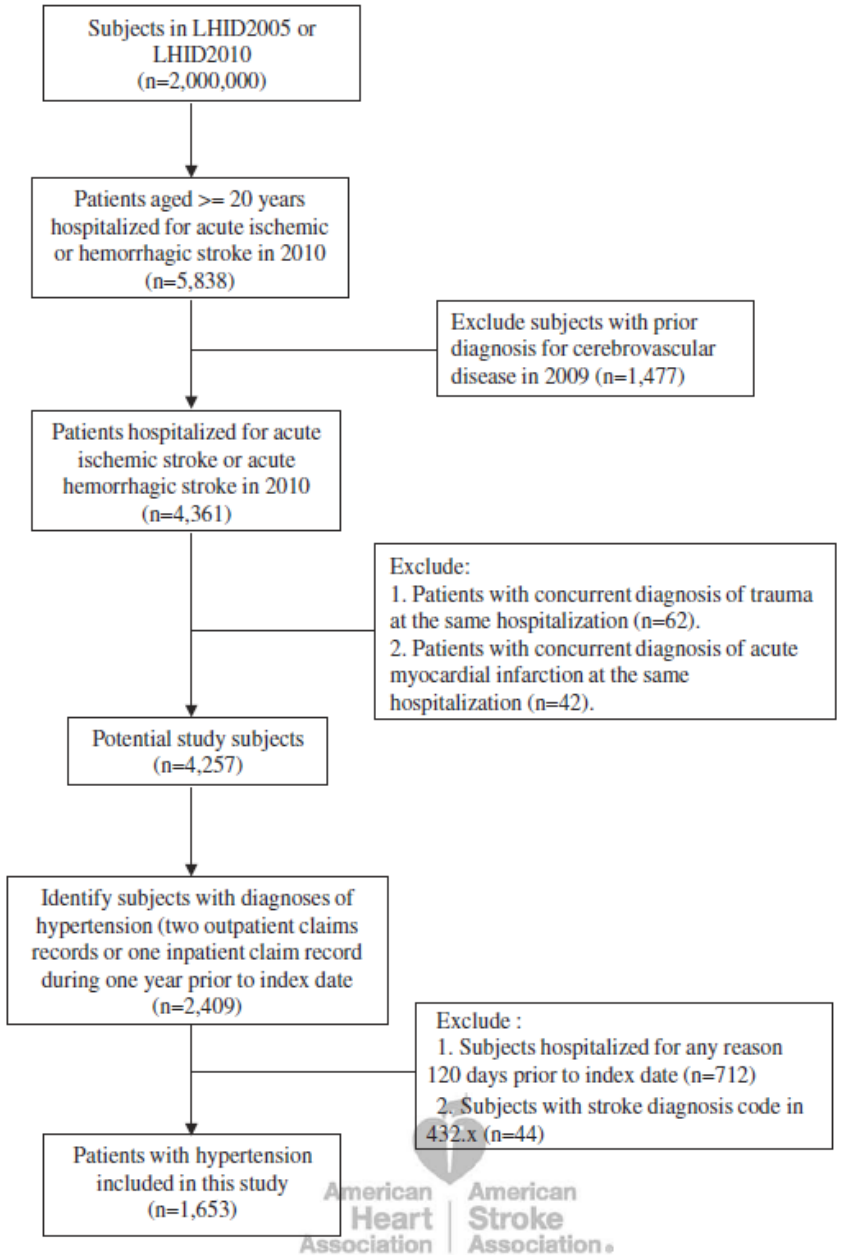


Figure 1. Flow diagram of inclusion/exclusion criteria for study population. LHID2005 indicates Longitudinal Health Insurance Database for the year 2005; and LHID2010, Longitudinal Health Insurance Database for the year 2010.

Chuang, S.-Y., et al., *Association of Short-Term Use of Nonsteroidal Anti-Inflammatory Drugs With Stroke in Patients With Hypertension.* Stroke, 2015. **46**(4): p. 996-1003.

Exposure to NSAIDs

- We identified information on NSAIDs use from prescription records in the NHIRD.
- NSAIDs classification
  - Selective COX-2 inhibitors (celecoxib and etoricoxib)
  - Nonselective NSAIDs
    - propionic acid derivatives (ibuprofen, ketoprofen, aproxen, flurbiprofen, tiaprofenicacid, fenoprofen, and fenbufen)
    - acetic acid derivatives (ketorolac, indomethacin, tolmetin, sulindac, etodolac, diclofenac, aceclofenac, and acemetacin)
    - fenamic acid derivatives (mefenamic acid)
    - enolic acid derivatives (piroxicam, meloxicam, and tenoxicam)
    - others(difunisal, nabumetone, nefopam, and nimesulide)
- Short term: 30-day period in this study.

Time-Varying Confounding Factors

- Upper respiratory tract infections
- Medications related to stroke
  - statins, antidiabetic agents (insulin, sulfonylurea, thiazolidinediones, and glinides), β-blockers, angiotensinconverting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, vitamin K antagonists, nonaspirin antiplatelet agents, aspirin
- number of outpatient visits

Data Analysis[1]

- A case-crossover design, an approach applied to investigate the effect of transient exposures on acute outcomes/events. each study patient served as his/her own control
- time-unvarying confounding factors were not adjusted in the subsequent analytic models.
- The odds ratios were computed using a pair-matched approach to evaluate the effect of NSAIDs use within the period right before the occurrence of stroke (case period) with a comparable period (control period).
  - **Case period:1 to 30 days before the index date**
  - **Control period: 91 to 120 days before the index date.**
- **Conditional logistic regression models** to examine the effect of NSAIDs use on stroke comparing between the case and control periods.
- Crude and adjusted odds ratios (AORs) were calculated, respectively, after controlling for the above time-varying confounding medication factors. I

Data Analysis[2]

- Subgroup analyses: To examine the modifying effect of various characteristics
  - Age
  - Sex
  - Charlson comorbidity index score
  - 10 heart disease (yes/no)
  - Type 2 diabetic mellitus (yes/no)
  - Anticoagulants use (yes/no)

- Also compared the odds of NSAIDs use between the case and control periods after the onset of stroke for ischemic or hemorrhagic stroke, separately.
- Sensitivity analyses-to test for the robustness of the results
  - 1 to 14 days before the index date as the case period and 15 to 28 days before the index date as the control period
  - 1 to 30 days before the index date as the case period and 31 to 60 days before the index date as the control period.

Table 1. Demographic and Clinical Characteristics of the Study Subjects

Characteristics	n	%
Demographics		
Age group, y		
20–64	470	28.4
≥65	1183	71.6
Sex		
Women	750	45.4
Men	903	54.6
Clinical characteristics		
Medical comorbid disorders (yes, %)		
Cerebrovascular disease	480	29.0
Chronic pulmonary disease	233	14.1
Type 2 diabetes mellitus	680	41.1
Heart failure	185	11.2
Conduction disorder	8	0.5
Valve heart disorders	61	3.7
Malignant neoplasm	88	5.3
Peripheral vascular disease	66	4.0
Upper respiratory tract infections	862	52.2
Osteoarthritis	404	24.4
Rheumatoid arthritis	13	0.8
Gout	217	13.1
Psychiatric comorbidity (yes, %)*	343	20.8
Concomitant medication		
Antidiabetes agents†	589	35.6
Antihypertensive agents		
ACE or ARB	1232	74.5
β-Blockers	985	59.6
Calcium channel blockers	1353	81.9
Diuretics	1034	62.6
Vitamin K antagonists	117	7.08
Others	394	23.8
Statins	600	36.3
Charlson comorbidity index score		
0–1	525	31.8
2–3	650	39.3
≥4	478	28.9
Healthcare use during 1 year before stroke		
No. of outpatient visits		
0	0	0.0
1–20	577	34.9
≥21	1076	65.1
No. of inpatient visits		
0	1393	84.3
≥1	260	15.7

ACE indicates angiotensin-converting enzyme; and ARB, angiotensin receptor blocker.

*Examined psychiatric comorbidities include dementia, mood disorder, schizophrenia and other psychosis, anxiety, and organic brain syndrome.

†Antidiabetic agents include insulin, sulfonylurea, thiazolidinediones, and glinides.

Table 2. Information Related to NSAIDs Use, Concomitant Medication Use, and Medical Use Between Case and Control Periods in the Study Subjects

Concomitant Medication	Case Period (1–30 d) n*	Case Period (1–30 d) %	Control Period (91–120 d) n	Control Period (91–120 d) %
Stroke (n=1653)				
NSAIDs use	529	32.0	395	23.9
Antidiabetes agents	462	27.95	413	24.98
Antihypertensive agents				
ACE or ARB	922	55.78	818	49.49
β-Blockers	742	44.89	649	39.26
Calcium channel blockers	1010	61.1	895	54.14
Diuretics	793	47.97	709	42.89
Vitamin K antagonists	93	5.63	77	4.66
Others	303	18.33	277	16.76
Statins	460	27.83	403	24.38
No. of outpatient visits				
0	200	12.1	363	21.96
1–2	662	40.05	720	43.56
≥3	791	47.85	570	34.48
Ischemic stroke (n=1395)				
NSAIDs use	453	32.47	329	23.58
Antidiabetes agents	411	29.46	360	25.81
Antihypertensive agents				
ACE or ARB	801	57.42	698	50.04
β-Blockers	624	44.73	538	38.57
Calcium channel blockers	862	61.79	748	53.62
Diuretics	685	49.10	600	43.01
Vitamin K antagonists	85	6.09	71	5.09
Others	262	18.78	236	16.92
Statins	416	29.82	361	25.88
No. of outpatient visits				
0	143	10.25	299	21.43
1–2	548	39.28	602	43.15
≥3	704	50.47	494	35.41
Hemorrhagic stroke (n=258)				
NSAIDs use	76	29.46	66	25.58
Antidiabetes agents	51	19.77	53	20.54
Antihypertensive agents				
ACE or ARB	121	46.9	120	46.51
β-blockers	118	45.74	111	43.02
Calcium channel blockers	148	57.36	147	56.98
Diuretics	108	41.86	109	42.25
Vitamin K antagonists	8	3.10	6	2.33
Others	41	15.89	41	15.89
Statins	44	17.05	42	16.28
No. of outpatient visits				
0	57	22.09	64	24.81
1–2	114	44.19	118	45.74
≥3	87	33.72	76	29.46

ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; and NSAIDs, nonsteroidal anti-inflammatory drugs.
*The study subjects are counted in both case period and control period,
respectively.

Conditional logistic regression models

Table 3 Risk of Stroke, Ischemic Stroke and Hemorrhagic Stroke, Respectively, in Relation to NSAIDs Use Among Patients With Hypertension

	Case Period		Control Period			
	With NSAIDs Use (n)	Without NSAIDs Use (n)	With NSAIDs Use (n)	Without NSAIDs Use (n)	COR (95% CI)	AOR (95% CI)*
Stroke (n=1653)						
Overall NSAIDs use	529	1124	395	1258	1.83† (1.51–2.21)	1.51† (1.23–1.85)
Selective NSAIDs	65	1588	55	1598	1.32 (0.83–2.11)	1.07 (0.65–1.76)
Nonselective NSAIDs	493	1160	361	1292	1.82† (1.50–2.21)	1.51† (1.24–1.86)
Diclofenac	217	1436	156	1497	1.64† (1.27–2.12)	1.43† (1.10–1.87)
Ibuprofen	69	1584	64	1589	1.10 (0.75–1.63)	0.91 (0.61–1.37)
Melenamic acid	104	1549	83	1570	1.36 (0.97–1.91)	1.19 (0.84–1.69)
Indomethacin	27	1626	19	1643	1.67 (0.82–3.41)	1.53 (0.74–3.19)
Sulindac	27	1626	19	1634	1.73 (0.82–3.93)	1.42 (0.66–3.04)
Ketorolac	47	1606	9	1644	5.75† (2.71–12.18)	4.79† (2.24–10.23)
Piroxicam	52	1601	49	1604	1.08 (0.69–1.70)	0.90 (0.56–1.44)
Meloxicam	69	1584	46	1607	2.00† (1.21–3.30)	1.59 (0.94–2.68)
Naproxen	19	1634	13	1640	1.86 (0.74–4.65)	1.55 (0.61–3.96)
Ketoprofen	12	1641	8	1645	1.67 (0.61–4.59)	1.22 (0.43–3.47)
Ischemic stroke (n=1395)						
Overall NSAIDs use	453	942	329	1066	1.94† (1.57–2.39)	1.57† (1.26–1.97)
Selective NSAIDs	59	1336	48	1347	1.42 (0.86–2.35)	1.08 (0.62–1.86)
Nonselective NSAIDs	420	975	301	1094	1.90† (1.54–2.34)	1.55† (1.24–1.94)
Diclofenac	181	1214	126	1269	1.71† (1.29–2.27)	1.48† (1.10–1.98)
Ibuprofen	59	1336	52	1343	1.18 (0.77–1.81)	0.99 (0.63–1.54)
Melenamic acid	93	1302	69	1326	1.48† (1.03–2.12)	1.31 (0.90–1.90)
Indomethacin	21	1374	11	1384	2.25 (0.98–5.17)	2.08 (0.88–4.89)
Sulindac	24	1371	14	1381	2.43† (1.01–2.85)	1.89 (0.77–4.67)
Ketorolac	36	1359	8	1387	5.00† (2.22–11.25)	4.31† (1.89–9.84)
Piroxicam	46	1349	42	1353	1.13 (0.69–1.85)	0.94 (0.56–1.57)
Meloxicam	61	1334	40	1355	2.00† (1.18–3.38)	1.50 (0.87–2.60)
Naproxen	16	1379	11	1384	1.83 (0.68–4.96)	1.54 (0.56–4.26)
Ketoprofen	11	1384	6	1389	2.00 (0.68–5.85)	1.48 (0.49–4.49)
Hemorrhagic stroke (n=258)						
Overall NSAIDs use	76	182	66	192	1.33 (0.83–2.14)	1.38 (0.79–2.40)
Selective NSAIDs	6	252	7	251	0.8 (0.22–2.98)	0.83 (0.21–3.36)
Nonselective NSAIDs	73	185	60	198	1.46 (0.91–2.37)	1.56 (0.90–2.73)
Diclofenac	36	222	30	228	1.33 (0.72–2.46)	1.33 (0.67–2.62)
Ibuprofen	10	248	12	246	0.78 (0.29–2.09)	0.73 (0.25–2.19)
Melenamic acid	11	247	14	244	0.63 (0.20–1.91)	0.58 (0.19–1.82)
Indomethacin	6	252	8	250	0.5 (0.09–2.73)	0.63 (0.10–4.10)
Sulindac	3	255	5	253	0.5 (0.09–2.73)	0.53 (0.10–3.03)
Ketorolac	11	247	1	257	11.00† (1.42–85.19)	12.98† (1.49–112.77)
Piroxicam	6	252	7	251	0.83 (0.25–2.73)	1.00 (0.28–3.63)
Meloxicam	8	250	6	252	2.00 (0.37–10.92)	3.92 (0.51–29.87)
Naproxen	3	255	2	256	2.00 (0.18–22.05)	1.76 (0.14–21.49)
Ketoprofen	1	257	2	256	NA	NA

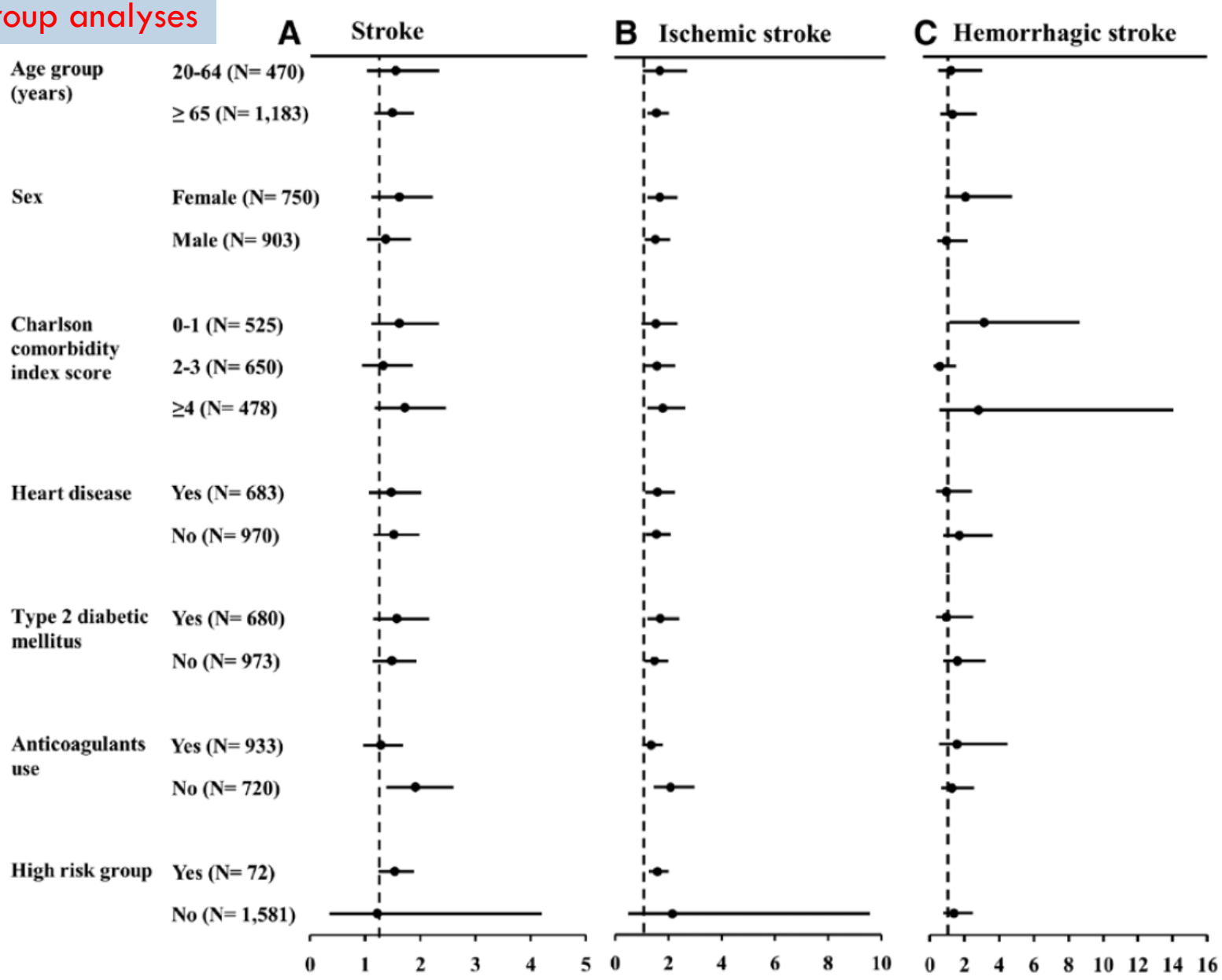
AOR indicates adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; NA, not available because of small sample size; and NSAIDs, nonsteroidal anti-inflammatory drugs.

*Covariates adjusted in the conditional logistic regression models include: upper respiratory tract infections, statins, antidiabetic agents, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, vitamin K antagonists, nonaspirin antiplatelet agents, aspirin, and number of outpatient visits.

†P value <0.05.

Figure 2 . Risk of stroke in relation to nonsteroidal anti-inflammatory drugs use among patients with hypertension, stratified by various demographic and clinical characteristics.

Subgroup analyses



Sensitivity test

Table 4 . Risk of Stroke in Relation to NSAIDs Use Among Patients With Hypertension, Based on Different Lengths for Case and Control Periods

	Case Period 1–14 d Control Period 15–28 d		Case Period 1–30 d Control Period 31–60 d		Case Period 1–30 d Control Period 91–120 d	
	COR (95% CI)	AOR (95% CI)*	COR (95% CI)	AOR (95% CI)	COR (95% CI)	AOR (95% CI)
Stroke						
Overall NSAIDs use	2.21† (1.72–2.82)	1.54† (1.18–2.00)	1.98† (1.60–2.46)	1.70† (1.36–2.13)	1.83† (1.51–2.21)	1.51† (1.23–1.85)
Selective NSAIDs	1.46 (0.72–2.96)	1.33 (0.63–2.82)	1.65 (0.90–3.01)	1.57 (0.84–2.96)	1.32 (0.83–2.11)	1.07 (0.65–1.76)
Nonselective NSAIDs	2.17† (1.70–2.78)	1.52† (1.16–1.98)	1.97† (1.59–2.44)	1.67† (1.34–2.10)	1.82† (1.50–2.21)	1.51† (1.24–1.86)
Ischemic stroke						
Overall NSAIDs use	2.19† (1.68–2.85)	1.52† (1.14–2.02)	2.03† (1.61–2.55)	1.74† (1.36–2.21)	1.94† (1.57–2.39)	1.57† (1.26–1.97)
Selective NSAIDs	1.80 (0.83–3.90)	1.71 (0.75–3.88)	1.69 (0.91–3.13)	1.49 (0.78–2.87)	1.42 (0.86–2.35)	1.08 (0.62–1.86)
Nonselective NSAIDs	2.15† (1.65–2.80)	1.49† (1.12–1.98)	1.98† (1.57–2.50)	1.69† (1.33–2.16)	1.90† (1.54–2.34)	1.55† (1.24–1.94)
Hemorrhagic stroke						
Overall NSAIDs use	2.33† (1.19–4.59)	1.86 (0.83–4.19)	1.72† (0.96–3.08)	1.40 (0.72–2.69)	1.33 (0.83–2.14)	1.38 (0.79–2.40)
Selective NSAIDs	0.33 (0.04–3.21)	NA	1.00 (0.06–16.00)	1.13 (0.06–20.71)	0.8 (0.22–2.98)	0.83 (0.21–3.36)
Nonselective NSAIDs	2.33† (1.19–4.59)	1.85 (0.83–4.13)	1.88† (1.05–3.39)	1.57 (0.81–3.04)	1.46 (0.91–2.37)	1.56 (0.90–2.73)

AOR indicates adjusted odds ratio; CI, confidence interval; COR, crude odds ratio; and NSAIDs, nonsteroidal anti-inflammatory drugs.

*Covariates adjusted in the conditional logistic regression models include: upper respiratory tract infections, statins, antidiabetic agents, β-blockers, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, calcium channel blockers, diuretics, vitamin K antagonists, nonaspirin antiplatelet agents, aspirin, and number of outpatient visits.

†*P* value <0.05.

對研究者的建議

- 熟悉資料庫的內容
- 思考研究主題並評估資料庫的可行性
- 由文獻回顧或專業意見找出重要的變項
- 與有經驗的資料庫使用者討論變項的定義
- 做中學

Thanks for your attention!