한국노년신경정신약물학회
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장소: 서울대병원 삼성안연구동 이건희 홀

Clinical Study using Big Data
- 건강보험 빅데이터를 활용한 임상연구 사례 소개

신주영
성균관대학교 약학대학

Pharmacoepidemiology

- Bridging science spanning both pharmacology and epidemiology
- Study of the utilization and effects of drugs in large numbers of people

- Effectiveness, safety and cost

Two study types

Drug utilization study

- Descriptive study
- Person, place, and time

Epidemiological study

- Causal association between drug and adverse events

Publications in psychopharmacology

- Drug Utilization Study
  - Pharmacoepidemiology and drug safety (2013, 2014)
  - Regulatory toxicology and pharmacology (2014, 2015, 2016)
  - British Journal of Clinical Pharmacology (2016)
  - Journal of Korean Medical Science (2011)

- Epidemiological Study
  - **BMJ (2016) (IF=19.967)**
  - **BMJ (2015) (IF=19.967)**
  - Gastroenterology (2016) (IF=16.716)
  - Drug Safety (2013, 2015)
  - PLoS One (2015a; 2015b)
  - Journal of psychopharmacology (2013, 2015)

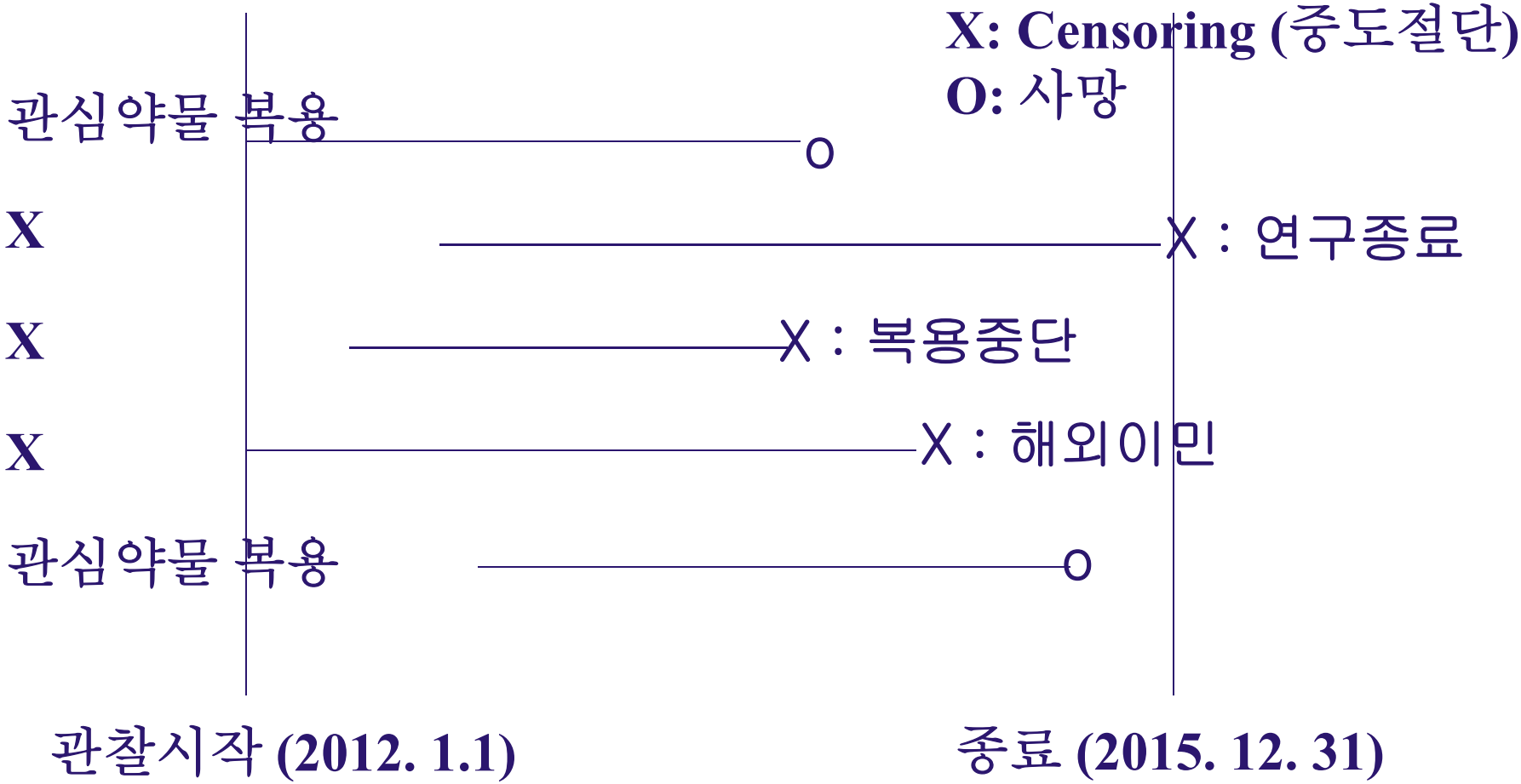
Research Example targeting elderly

- **Drug Utilization Study**
  - Polypharmacy 현황 (PloS One 2014)
  - 노인 장기지속형 벤조다이아제핀 (Int J Clin Pharmacol Ther 2017)
    - 독일, 한국 비교 연구

- **Epidemiological Study**
  - 항우울약물과 해열진통소염제의 병용사용으로 인한 뇌출혈 등 코호트연구
  - 항정신병약물의 허혈성뇌졸중 관련성 확인을 위한 환자교차군 연구 (Journal of psychopharmacology, 2013, 2015)

Evidence Pyramide

코호트연구,
1) 약물노출 확인 , 2) 추적관찰



코호트연구의 연구질문예시

- 죽느냐? 사느냐?
- 어떤 약을 먹고 부작용이 발생하느냐? 안하느냐?
  - (예시) 진통제와 항우울제를 병용해서 복용하여 뇌출혈 위험이 올라가는가?
  - (예시) 항정신병약물 종류에 따라서 허혈성뇌졸중 발생률이 달라지는가?
- 특정 약물이 비교약물에 비해서 특정 효과가 더 좋은가, 안 좋은가?

코호트연구와 상대위험도

부작용발생 여부	약물 종류 A	약물 종류 B
발생 O	A	B
발생 X	C	D
대상수	N_1	N_0
관찰기간총합	T_1	T_0

A 복용집단의
부작용발생률: $A/T_1 = I_1$

B복용집단의
부작용발생률: $B/T_0 = I_0$

분석 지표	분석 내용
상대위험도(RR) ; 발생률의 비 Relative Risk (Rate)	$RR=I_1/I_0$

코호트연구자료의 형태

- 부작용발생 (결과변수, Y)
  - 발생여부(Y1)
    - 발생했느냐? 안했느냐? (이분형변수)
  - 관찰기간(Y2)
    - 발생한 경우: 부작용 발생 때까지의 관찰기간
    - 발생하지 않은 경우: 실제 관찰기간
- 의심되는 약물 및 교란요인 (X)
  - 부작용 발생과 관련된 여러 요인(특성)들
  - 의심약물복용여부, 연령, 성별 등 다양한 형태로 포함

OPEN ACCESS

Risk of intracranial haemorrhage in antidepressant users with concurrent use of non-steroidal anti-inflammatory drugs: nationwide propensity score matched study

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Accepted: 16 June 2015

ABSTRACT

OBJECTIVE
To define the risk of intracranial haemorrhage among patients treated with antidepressants and non-steroid anti-inflammatory drugs (NSAIDs), compared with the risk among those treated with antidepressants without NSAIDs.

DESIGN
Retrospective nationwide propensity score matched cohort study.

SETTING
Korean nationwide health insurance database between 1 January 2009 and 31 December 2013.

PARTICIPANTS
Patients who began receiving antidepressants for the first time (index date) without a history of having received a prescription for antidepressants during the preceding year. Patients who had been diagnosed as having cerebrovascular diseases within a year before the index date were excluded.

MAIN OUTCOME MEASURE
Time to first hospital admission with intracranial haemorrhage within 30 days after drug use. Matched Cox regression models were used to compare the risk of intracranial haemorrhage among patients who were treated with antidepressants with and without NSAIDs, after propensity score matching with a 1:1 ratio.

RESULTS
After propensity score estimation and matching in a 1:1 ratio, the cohort used in the analysis included 4 145 226 people. The 30 day risk of intracranial haemorrhage during the entire study period was higher for combined use of antidepressants and NSAIDs than for use of antidepressants without NSAIDs (hazard ratio 1.6, 95% confidence interval 1.32 to 1.85). No statistically meaningful differences were found in risk of intracranial haemorrhage between the antidepressant drug classes.

CONCLUSIONS
Combined use of antidepressants and NSAIDs was associated with an increased risk of intracranial haemorrhage within 30 days of initial combination.

WHAT IS ALREADY KNOWN ON THIS TOPIC
Antidepressants and non-steroidal anti-inflammatory drugs (NSAIDs) are generally believed to each increase the risk of abnormal bleeding
However, very little is known about the risk of intracranial haemorrhage associated with the combined use of antidepressants and NSAIDs

WHAT THIS STUDY ADDS
Combined use of antidepressants and NSAIDs was associated with an increased risk of intracranial haemorrhage within 30 days of initial combination

Introduction
Depression produces the greatest decrement in health of all common chronic conditions,[1] and depression in older people is an important public health problem.[2] Antidepressants can help depressive patients effectively, but concern exists that antidepressants may interact unfavourably with non-steroidal anti-inflammatory drugs (NSAIDs).[3 4]

Antidepressants, especially selective serotonin reuptake inhibitors, and NSAIDs are each thought to increase the risk of abnormal bleeding.[5 6] According to the results of a meta-analysis in 2008, the odds ratio of upper gastrointestinal haemorrhage was 2.36 (95% confidence interval 1.44 to 3.85) for selective serotonin reuptake inhibitors alone and 6.33 (3.40 to 11.82) with concomitant NSAIDs,[7] although controversy exists about whether the risk of gastrointestinal bleeding increases when they are prescribed together, compared with their use alone.[8 9]

Unlike for gastrointestinal bleeding, neither selective serotonin reuptake inhibitors nor NSAIDs alone have been found to be associated with an increased risk of intracranial haemorrhage.[10-13] However, little is known about the risk of intracranial haemorrhage associated with the combined use of antidepressants and NSAIDs. We sought to estimate the risk of intracranial haemorrhage among patients who were treated with both antidepressants and NSAIDs, compared with the risk among those treated with antidepressants without NSAIDs.

Methods
Data source
We used the Korean Health Insurance Review and Assessment Service database for this study. The National Health Insurance programme started in Korea in 1977 and achieved universal coverage of the population by 1989.[14] All Koreans are covered by the programme. Accordingly, the database contains all information on healthcare use and prescribed drugs for approximately 50 million Koreans.

We obtained the claims data for the patients who were prescribed at least one antidepressant drug from 1 January 2009 to 31 December 2013. The database included an unidentifiable code representing each patient together with age, sex, diagnosis, ambulatory

Background

- Antidepressant, SSRIs block platelet uptake, and results in bleeding complications,
  - However, SSRIs alone were not associated with an increased risk of intracranial hemorrhage in the previous studies[1-3)]

+

- NSAIDs are also known to inhibit normal platelet function,
  - However, NSAIDs alone were not associated with an increased risk of intracranial haemorrhage in the previous study[4)]

?

- We raised the question, how about the risk of intracranial haemorrhage when we use both drugs together?

1) Bak S, et al (2002); 2) de Abajo FJ, et al (2000); 3) Kharofa J, et al (2007); 4) Johnsen SP, et al (2003)

Objective

- **We aimed to define the risk of intracranial haemorrhage among patients who were treated with antidepressants and NSAIDs, as compared with the antidepressants alone.**

Data sources

- **Korea Health Insurance Review & Assessment Service (HIRA) Database**
  - **Covers whole population of approx. 50 million in South Korea**
  - **The claims data with at least one prescription of antidepressants from January 1, 2008, through December, 31, 2012**

Patient characteristics	Diagnosis	Prescription
Anonymised patient code	Visit date	Rx date
Age	Institution Code	
Gender	Ambulatory/Hospitalization	Drug name, Formula
Geographic region	Emergency Department visit	
		Duration, Dose
	Diagnosis (ICD-10)	

Study design & subjects

- Study design: Retrospective cohort study
- Study subjects
  - Inclusion criteria
    - The patients who were newly prescribed antidepressants for the first time without a history of antidepressants within one year before the index date.
  - Exclusion criteria
    - The patients with cerebrovascular diseases (ICD-10: I60-I68, G45, G46) as their primary or secondary diagnosis
    - Patients who were over the age of 99
    - Patients who were diagnosed with intracranial haemorrhage on the index date

Study drug

- **Antidepressants classification**
  - Tricyclic antidepressants (TCAs)
  - Selective serotonin reuptake inhibitors (SSRIs)
  - Serotonin-norepinephrine reuptake inhibitors (SNRIs)
  - Monoamine oxidase inhibitors (MAOIs)
  - Others

- **Combined use of NSAIDs**
  - The prescription of at least one NSAIDs (ATC code: M01A, N02BA, more than 325 mg of acetylsalicylic acid per tablet) during the defined 30 day follow-up of antidepressants.

Follow-up to intracranial hemorrhage

- **Index date**
  - The date of newly prescribed antidepressants in both groups
  - Assumed follow-up of antidepressants last for 7 days after the final prescription in continuous course

- **Outcome definition**
  - First hospitalization due to the intracranial haemorrhage (ICD-10: I60-62) with their primary or secondary diagnosis within 30 days' follow-up after the index date

- **Censoring**
  - The date of antidepressant discontinuation, switching to another, and the last date of the study *whichever comes first*

Potential Confounders

- Age, gender
- Charlson comorbidity index
- Comorbidity
  - Diabetes, hypertension, dyslipidemia, arthritis, COPD, osteoporosis, alcohol-related disorder, ischemic heart disease, chronic kidney disease, cerebrovascular disease, dementia
- Co-medication
  - Low-dose aspirin
  - Antithrombotic agents (ATC B01A)
    - Vitamin K antagonists(ATC B01AA): warfarin, et al.
    - Heparin group (ATC B01AB): heparin, enoxaparin, et al.
    - Platelet aggregation inhibitors(ATC B01 AC)
      : clopidogrel, prasugrel, cilostazol, ticlopidine, et al.
    - Enzymes (ATC B01AD): streptokinase, alteplase, et al.
    - Direct thrombin inhibitors, Direct factor Xa inhibitors, et al.

Korean Stroke Guideline. 2009; Donnan et al. 2008

Propensity-matched cohort

- Propensity score was estimated using multiple logistic regression.
  - *A full non-parsimonious model* was developed that included all the variables including potential confounders
  - Model discrimination was assessed with *c statistics* (0.6-0.8).
- Matching was performed using Greedy 5→1 Digit Matching Macro.

Statistical analysis

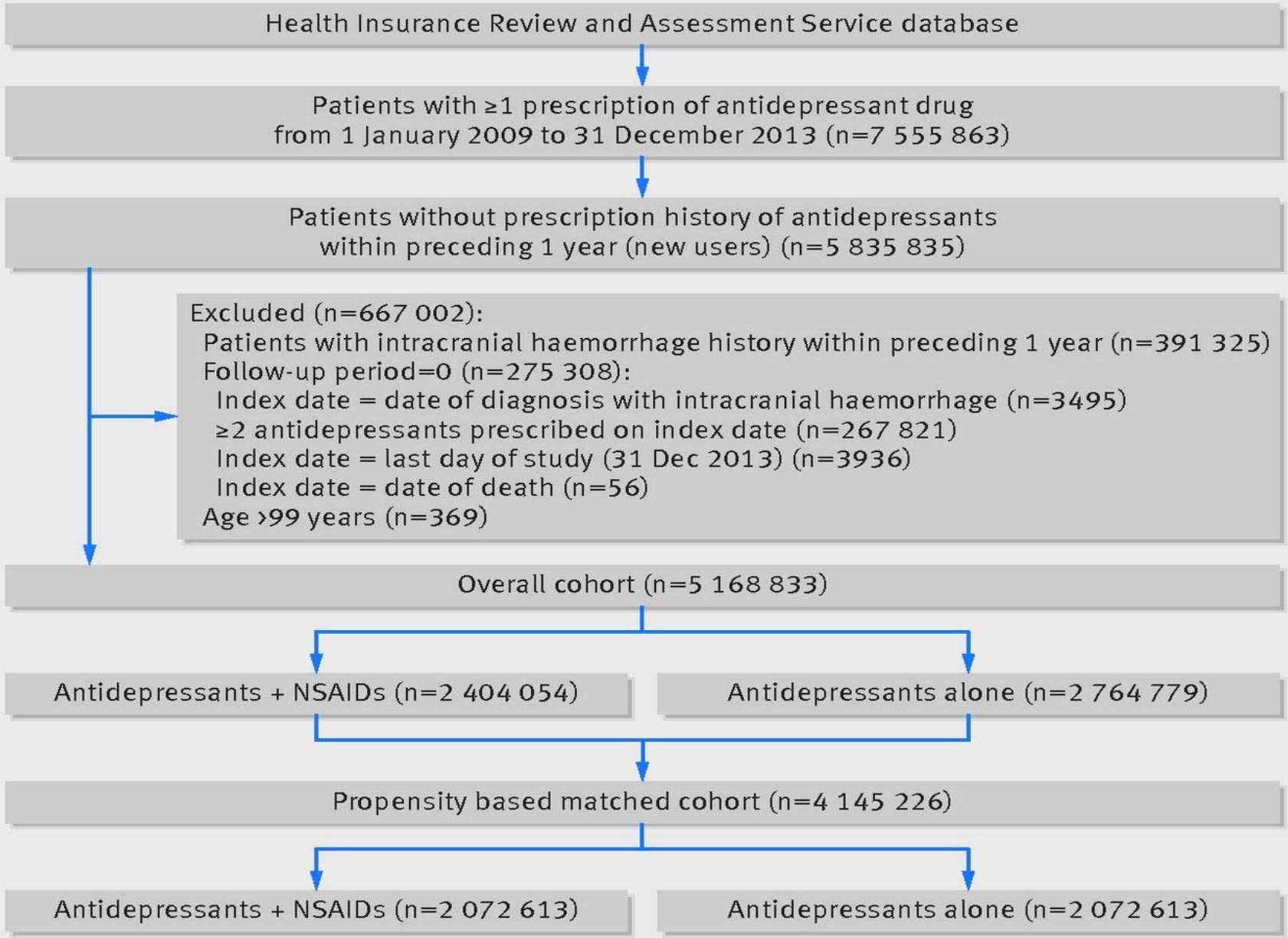
- Distribution of characteristics among overall cohort and propensity-matched cohort
    - Antidepressants alone vs. Antidepressants with NSAIDs
        - Imbalance was defined as an absolute value greater than 0.1 using the Standardized Difference

- Incidence rate (IR) per 1,000 person-years and its 95% confidence interval (CI) assuming a Poisson distribution.

Statistical analysis

- The hazard ratios (HRs) and their 95% CIs for hemorrhagic stroke using the Cox regression models
  - Antidepressants alone vs. antidepressants with NSAIDs
  - Adjusted HRs
    - Construction of multivariable model using likelihood ratio test
      - The final model included dementia, warfarin, heparin group, and steroids as the adjusting variables
      - Assess the status of combined use of NSAIDs and covariates on a daily basis during the follow-up time for the time varying covariates
  - Death was treated as competing risk rather then censoring

Study flowchart



Baseline characteristics (1)

	Overall cohort			PS-matched cohort		
	Alone (n=2,764,779)	Combined (n=2,404,054)	SD	Alone (n=2,072,613)	Combined (n=2,072,613)	SD
Age, mean (SD)	48.4 (18.4)	54.2 (16.16)	0.328	52.2 (16.6)	52.3 (16.6)	0.006
Male, (%)	40.3	36.1	-0.013	38.9	38.4	0.001
Charlson, median (IQR)	0 (0-1)	1 (0-1)	0.073	1 (0-1)	1 (0-1)	0.002
History of comorbidities in previous year						
Diabetes	11.5	13.7	0.066	12.5	12.7	0.004
Hypertension	23.1	30.1	0.158	26.6	26.9	0.006
Osteoarthritis	15.4	30.6	0.365	20.4	20.6	0.005
Rheumatoid Arthritis	1.5	3.8	0.145	1.9	2.0	0.003
Osteoporosis	6.1	10.7	0.167	7.7	7.8	0.005
Ischaemic heart disease	5.0	5.7	0.031	5.3	5.4	0.003

Baseline characteristics (2)

	Overall cohort			PS-matched cohort		
	Alone	Combined	SD	Alone	Combined	SD
Drug use in previous year						
Low dose aspirin	11.1	14.1	0.090	12.5	12.7	0.005
Warfarin	48.7	61.0	0.250	56.7	56.9	0.006
Heparin group	0.5	0.5	-0.003	0.5	0.5	0.001
Platelet aggregation inhibitors	2.2	2.4	0.010	2.2	2.2	0.001
Antithrombotic enzymes	5.4	7.0	0.067	6.1	6.2	0.003

*No differences in distribution of direct thrombin inhibitors, direct factor Xa inhibitors, other antithrombotic agents, and steroid

Risk of 30 day intracranial haemorrhage with combined use of antidepressants and NSAIDs, compared with antidepressant alone

	Antidepressants Alone IRs (95% CI)	Antidepressants + NSAIDs, Combined IRs (95% CI)	Adjusted hazard ratio (95% CI)	P value
Overall	1.6 (1.36 to 1.84)	5.7 (5.28 to 6.22)	1.6 (1.32 to 1.85)	<0.01
Antidepressant exposure				
TCA	1.5 (1.16 to 1.95)	5.8 (5.18 to 6.48)	1.7 (1.33 to 2.13)	0.770
The rest	1.6 (1.35 to 1.95)	5.7 (5.02 to 6.39)	1.6 (1.27 to 2.03)	
SSRI	1.3 (0.93 to 1.79)	6.8 (5.50 to 8.48)	1.4 (1.17 to 1.72)	0.678
The rest	1.7 (1.42 to 1.99)	5.6 (5.11 to 6.10)	1.5 (1.27 to 1.86)	
SNRI	4.3 (2.55 to 7.26)	4.4 (2.51 to 7.78)	0.4 (0.32 to 0.46)	0.190
The rest	1.5 (1.28 to 1.75)	5.8 (5.31 to 6.27)	1.5 (1.31 to 1.83)	

Discussion

- **Additive effect** according to the drug-drug interaction
  - The addition of NSAIDs to antidepressant treatment increased the risk of intracranial haemorrhage in our study.

- SSRIs block platelet uptake, and results in bleeding complications,
  - However, SSRIs alone were not associated with an increased risk of haemorrhage in the previous studies[1-3)]

+

- NSAIDs are also known to inhibit normal platelet function,
  - However, NSAIDs alone were not associated with an increased risk of haemorrhage in the previous study[4)]

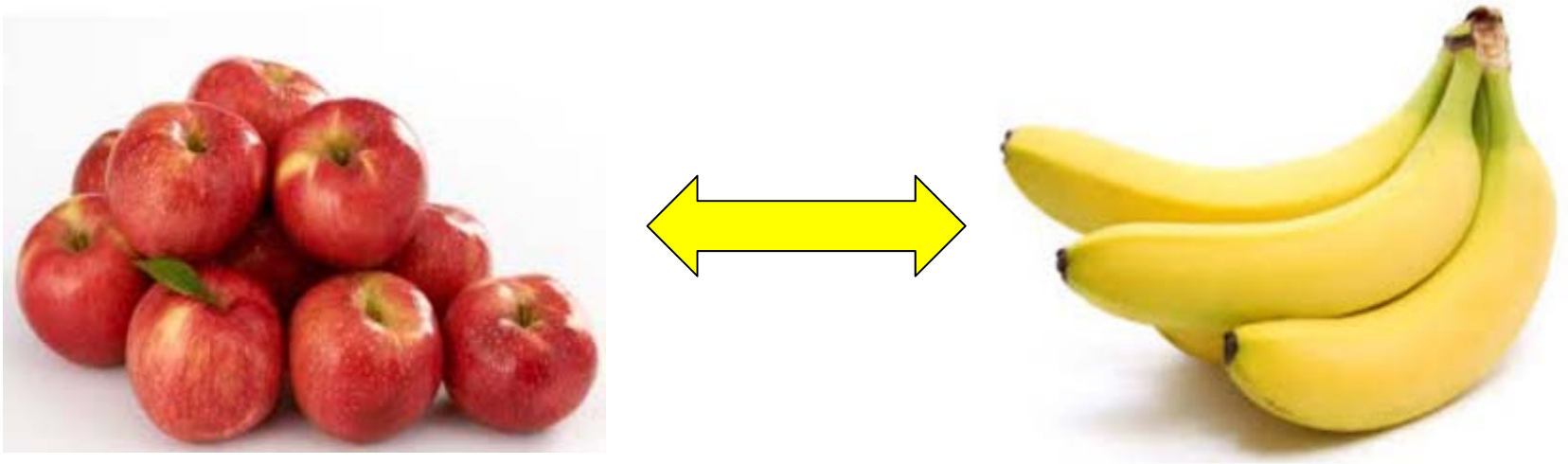
1) Bak S, et al (2002); 2) de Abajo FJ, et al (2000); 3) Kharofa J, et al (2007); 4) Johnsen SP, et al (2003)

Discussion

- Advancing age and antithrombotic agents are well know risk factors for intracranial haemorrhage
  - The combined use of antidepressants and NSAIDs seems not to have had a major effect on patients who already had risk factors for intracranial haemorrhage.
  - The endpoint not related to bleeding, myocardial infarction was tested in the same setting, the risk was not increased (hazard ratio 0.9, 0.65 to 1.32).

환자교차군연구

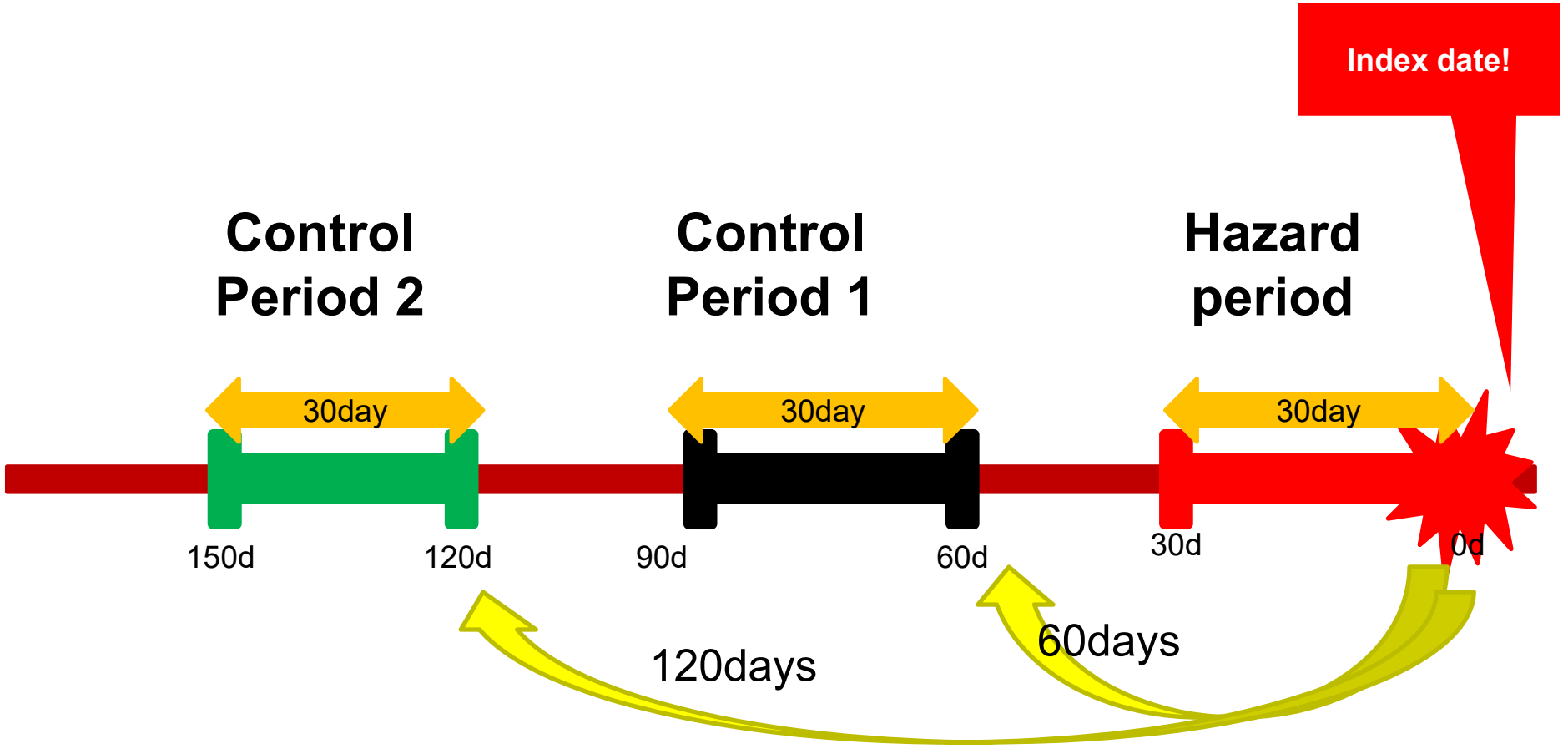
Case-based design의 적용



- 관심약을 먹은 사람과 비교약을 먹은 사람은 동반질환, 병용약물 등을 비롯한 특징이 너무 다르다. 사과와 바나나를 비교하는 것이 말이 되는가?
  (극복방법) 매칭, 성향점수(Propensity score) 적용
  그러나, 여전히 부족하다…….

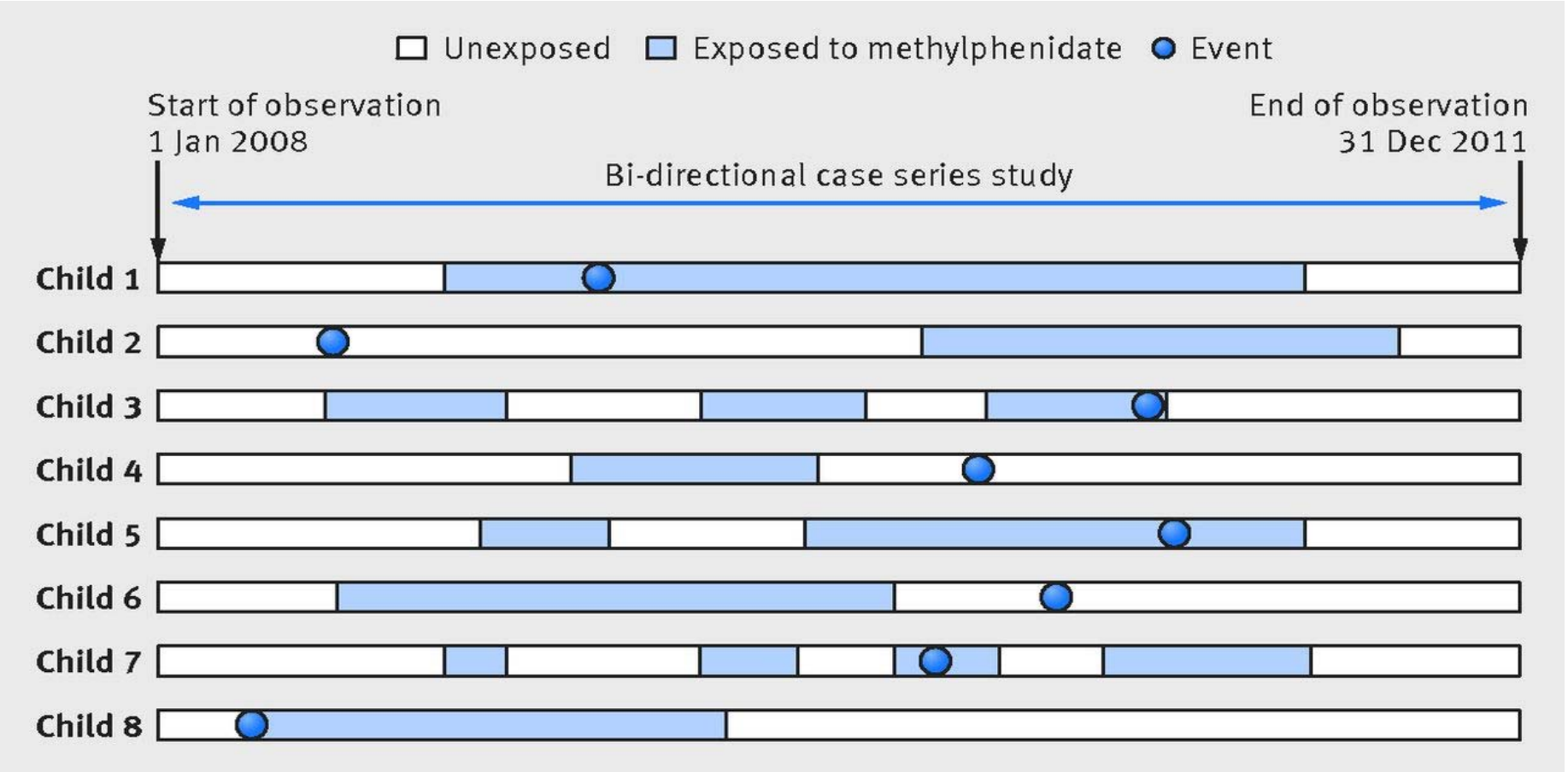
Case-based design의 적용(1)
Case-crossover study

- 환자교차군 연구 (환자-대조군 연구의 변형)



Case-based design의 적용(2)
Self controlled case series study (SCCS)

- 코호트연구의 변형



환자교차군연구와 SCCS의 통계분석방법

- **환자교차군**
  - 조건부로지스틱회귀분석을 통한 OR값과 95% 신뢰구간 제시

- **자가통제환자군(SCCS)**
  - 상대위험도값을 추정해야 함
  - 생존분석 중,
  - 콕스모델을 적용한 Hazard Ratio와 95% 신뢰구간
  - 포와송회귀분석을 적용한 Rate Ratio와 95% 신뢰구간

Atypical Antipsychotics for the Risk of Ischemic Stroke among Korean Elderly Population

Original Paper

Risk of ischemic stroke with the use of risperidone, quetiapine and olanzapine in elderly patients: a population-based, case-crossover study

Psychopharm

Journal of Psychopharmacology
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DOI: 10.1177/0269881113482530
jop.sagepub.com
SAGE

Ju-Young Shin[1], Nam-Kyong Choi[2], Sun-Young Jung[3], Joongyub Lee[2], Jun S Kwon[4] and Byung-Joo Park[1,2,3,5]

Abstract

We conducted a case-crossover study to evaluate the comparative risk of ischemic stroke associated with the use of risperidone, quetiapine and olanzapine in geriatric patients using the Korean Health Insurance Review and Assessment Service database. Cases included elderly patients >64 years old who had experienced their first ischemic stroke (International Classification of Disease, Tenth Revision (ICD-10), I63) hospitalization from July 2005 to June 2006 and who had been without prior cerebrovascular diseases (ICD-10, I60–I69), or transient ischemic attack (ICD-10, G45). Exposures to risperidone, quetiapine and olanzapine were assessed during the 30 days prior to the stroke episode. We set two control periods with lengths which were the same as the hazard periods. Adjusted odds ratios (aORs) with 95% confidence intervals (CIs) were estimated by conditional logistic regression. A total of 1601 cases of ischemic stroke with a mean age of 75.6 (±6.7) years were identified, among which 933 (58.3%) were female. An increased risk of ischemic stroke was associated with the use of risperidone (aOR=3.5, 95% CI 3.3–4.6) and quetiapine (aOR=2.7, 95% CI 2.0–3.6) during the 30 days prior to stroke: however, no significant risk was observed with olanzapine (aOR=1.2, 95% CI 0.7–2.0). The increased stroke risk in demented patients, assessed within 30 days after exposure, was also observed with olanzapine. However, the sample of olanzapine users was small and underpowered.

Keywords

Atypical antipsychotics, ischemic stroke, case-crossover, national health insurance claims database

Atypical Antipsychotics

- **Atypical Antipsychotics: AAP**
  - **Serotonin-Dopamin D2 Antagonist**
    - **Widely used since the 1990s**
  - **Marketed as offering greater efficacy**
  - **Reducing side effect**
    - **Extrapyramidal symptoms**
  - **Commonly prescribed and recommended**
    - **As a first-line treatment for schizophrenia**
    - **BPSD in demented patients**

Katzung's Clinical Pharmacology-Basic & Clinical Pharmacology 8 th edition. 2001; Mazzucco S et al. 2008; Motsinger et al. 2003.

AAP Safety Issues

2002	Canada health regulatory agency Risperidone: Increased risk of CVAEs in clinical trials of elderly demented patients
2003	The USA FDA Warning Risperidone: Required changes in prescribing information
2004	EMEA Olanzapine: Increased risk of CVAEs and mortality in the elderly with dementia
2004	UK MHRA Risperidone and Olanzapine: Increased risk of stroke in the dementia to treat BPSD
2005	The USA FDA Warning Aripiprazole: Increased risk of CVAEs and mortality in the elderly with dementia

Increasing controversy (2005~)

- **Clinical Uncertainty**
  - Systematic review, risperidone and the risk of stroke : conflicting findings 1)
  - Olanzapine is safe! 2, 3)

- **Limitation of previous research**
  - Unmeasured confounding
  - Difference of underlying disease, life style
  - Difference of concomitant medication

1) Mazzucao etal. 2008;
2) Moretti R et al. 2005; 3) Yulug B et al. 2009;

The Necessity of Additional Observational Study

- **Limitation of previous research**
  - Simultaneous investigation of CVAEs
    - Different Mechanism of Ischemic Stroke
  - Dose-response fashion of AAP with Ischemic Stroke
  - The effect of dementia : uncertain as a modifier

- **Well-designed study should be performed to identify the type of AAPs and ischemic stroke association controlling bias.**

Objective

- **To estimate the risk for ischemic stroke in elderly users of AAPs**
  1) ***To compare the difference of risk between AAPs generic drugs***
  2) ***To evaluate the dose-response relationship***
  3) ***To identify the dementia as a effect modifier***

Method: data source

- **Korea Health Insurance Review & Assessment Service (HIRA) database for elderly population**
  - **Between 1 Jan 2005 and 30 June 2006**
  - **Covers whole elderly population of approx. 4,000,000 in South Korea**
  - **Information**

Patient characteristics	Diagnosis	Prescription
Anonymised patient code	Visit date	Rx date
Age	Institution Code	
Gender	Ambulatory/Hospitalization	Drug name, Formula
Geographic region	Emergency Department visit	
		Duration, Dose
	Diagnosis (ICD-10)	

Atypical Antipsychotics

Generic name	Class	WHO ATC code
Amisulpride	Benzamides	N05AL05
Aripiprazole	Other APs	N05AX12
Clozapine	Diazepines, oxazepines and thiazepines	N05AH02
Olanzapine	Diazepines, oxazepines and thiazepines	N05AH03
Quetiapine	Diazepines, oxazepines and thiazepines	N05AH04
Risperidone	Other APs	N05AX08
Ziprasidone	Indole derivatives	N05AE04
Zotepine	Other APs	N05AX11

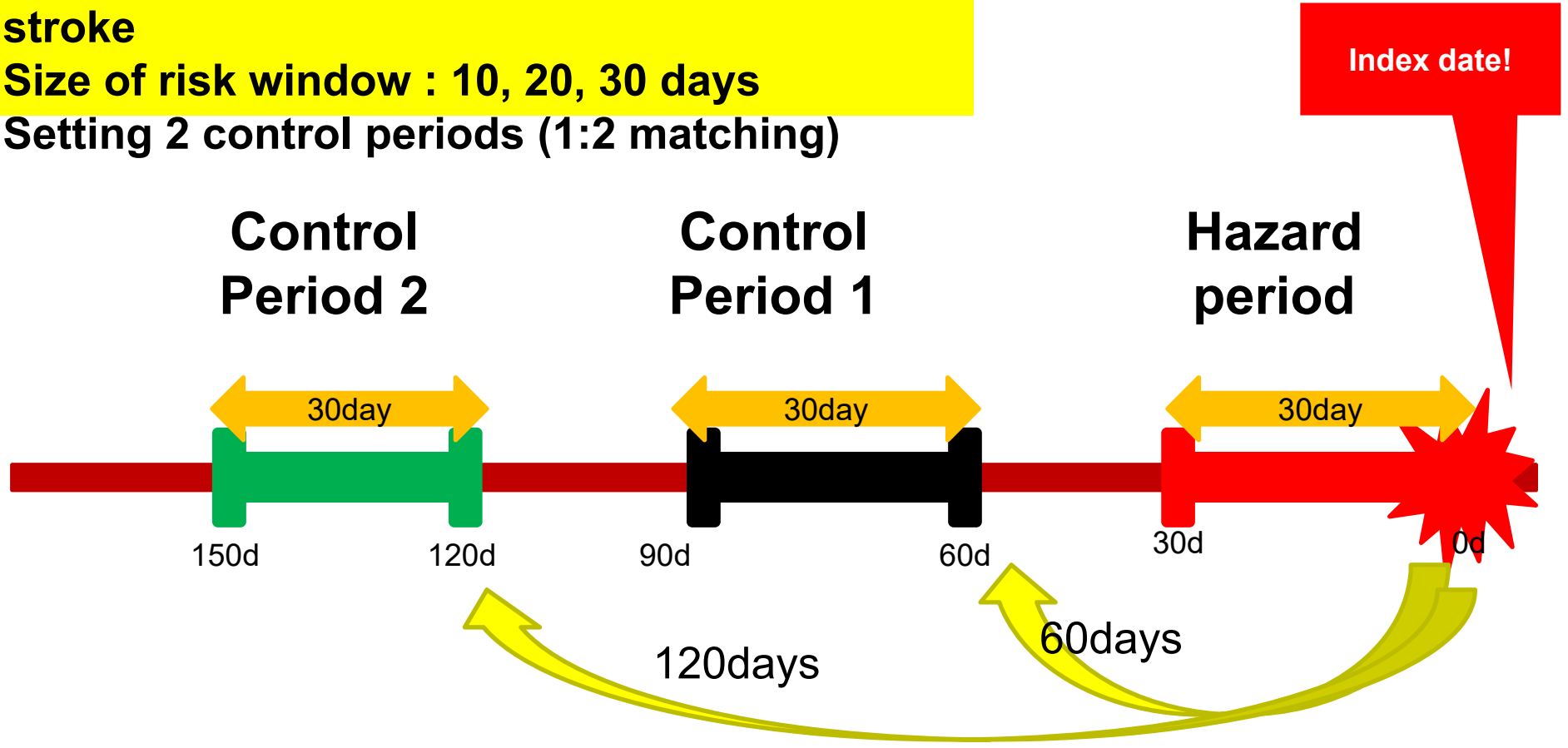
Selection of Study population

- **Case definition**
  - Age>65
  - Ischemic Stroke as main diagnosis
    - **2005/7/1~2006/6/30 ,Ischemic Stroke (I63) first hospitalization**
    - **Index date: first stroke occurrence date**
  - Patients with prescription of AAP

- **Exclusion Criteria**
  - CVA admission: 6month prior to index date
  - Prescription data afterward the index date
  - Incorrect exposure data

Case Crossover Design

Index date: First diagnosis of ischemic stroke
Size of risk window : 10, 20, 30 days
Setting 2 control periods (1:2 matching)



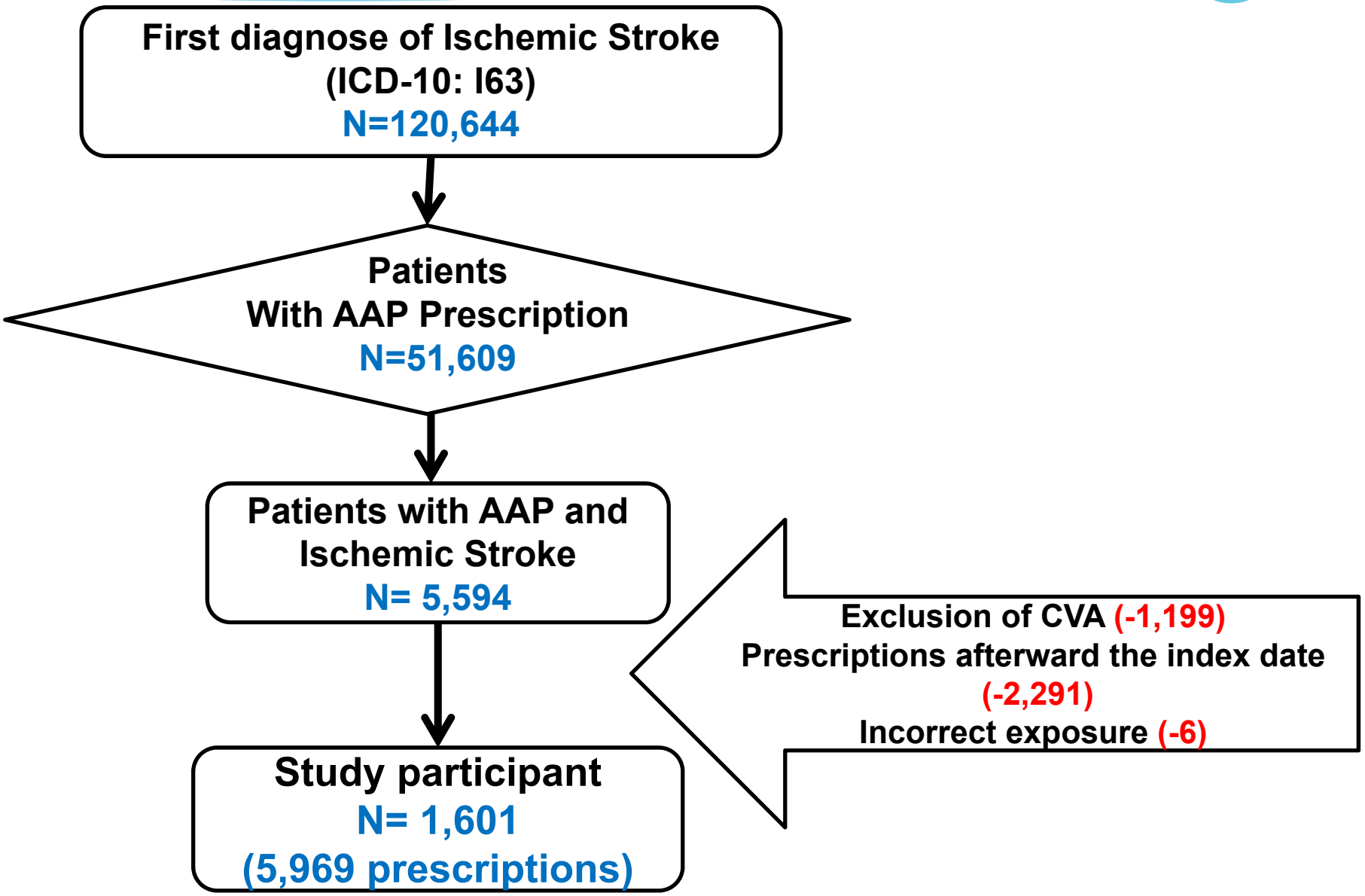
Possible confounders affecting Stroke

- **Time invariant confounders**
  - Life Style Factors
    - Smoking, alcohol, obesity, etc
  - Co-morbidity
    - Diabetes, hypertension, dementia, heart failure, COPD, etc
- **Time variant confounder**
  - Co-morbidity
    - Infective endocarditis, valvular heart disease, pneumonia, acute myocardial infarction, thyrotoxicosis, thromboembolism, atrial fibration
  - Co-medication
    - Anti-coagulants (warfarin, heparin, antithrombin III, dalteparin, etc)
    - Oral antithrombotic agents (streptokinase, alteplase, urokinase, etc)

Statistical Analysis

- **Descriptive analysis: frequency & proportion**
  - Age, gender, region, type of institution
  - Prescribed generic drugs of AAPs
  - Presence of dementia, co-morbidity, co-medication affecting stroke
- **Conditional logistic regression: *adjusted* OR, 95% CI**
  - Risk of ischemic stroke for the AAPs
  - Risk of ischemic stroke between generic drugs of AAPs
- **Stratified Analysis**
  - Dose of prescribed AAPs: using the WHO-DDD Index
  - Dementia as a effect modifier
- **Sensitivity Analysis**
  - Size of risk window: 30 day, 20 day, 10 day

Flow chart of process to select cases



General characteristics of study subject (1)

Characteristics	No. of Subjects (N=1,601)	(%)
Mean Age (yr) (SD)	75.57 (6.7)	
Female Gender	933	41.7
Region*		
Urban	1,944	66.3
Rural	576	19.6
Intermediate	413	14.1
Type of Institution*		
Primary	872	50.5
Secondary	626	36.3
Tertiary	229	13.2
Atypical Antipsychotics*		
Risperidone	1,154	64.7
Quetiapine	429	24.1
Olanzapine	146	8.2
Others	54	3.0

* Patients included in each type of region, medical institutions, prescribed drugs of AAPs were not mutually exclusive.

General characteristics of study subject (2)

Characteristics	No. of Subjects (N=1,601)	(%)
Presence of dementia (F00-03, G30,G31.8)	1,097	68.5
Comorbidity affecting risk of stroke		
Valvular heart disease (I06-I08)	10	0.6
Acute myocardial infarction (I21)	94	5.9
Thyrotoxicosis (E05)	71	4.4
Pneumonia (J12-J18)	405	25.3
Atrial fibrillation (I48)	121	7.6
Concurrent use of medications*		
Anti-coagulants	401	25.0
Oral antithrombotic agents	64	4.0

* Patients included in each type of region, medical institutions, prescribed drugs of AAPs were not mutually exclusive.

Risk of Ischemic Stroke for the AAPs

AAPs	No. of Hazard Period Exposure (n=1,601)	No. of Control Period Exposure (n=3,202)	Unadjusted OR (95% CI)	Adjusted OR* (95% CI)
Exposure access within 30 days before stroke incidence				
Any AAP user	998	1,119	3.9 (3.4-4.5)	1.7 (1.5-2.1)
Risperidone	687	717	3.9 (3.3-4.7)	1.8 (1.5-2.3)
Quetiapine	250	292	3.5 (2.6-4.6)	1.7 (1.2-2.3)
Olanzapine	77	112	2.1 (1.4-3.4)	1.0 (0.5-1.9)
Exposure access within 20 days before stroke incidence				
Any AAP user	324	1,210	3.1 (2.7-3.6)	1.8 (1.5-2.1)
Risperidone	636	781	3.3 (2.8-3.9)	1.8 (1.5-2.2)
Quetiapine	226	315	2.5 (1.9-3.4)	1.6 (1.2-2.2)
Olanzapine	70	113	1.8 (1.1-3.0)	1.0 (0.5-1.8)
Exposure access within 10 days before stroke incidence				
Any AAP user	799	1,308	1.9 (1.6-2.2)	1.6 (1.3-1.9)
Risperidone	538	865	1.9 (1.6-2.3)	1.8 (1.4-2.1)
Quetiapine	201	333	1.8 (1.3-2.4)	1.6 (1.1-2.1)
Olanzapine	60	114	1.2 (0.6-2.2)	0.9 (0.5-1.7)

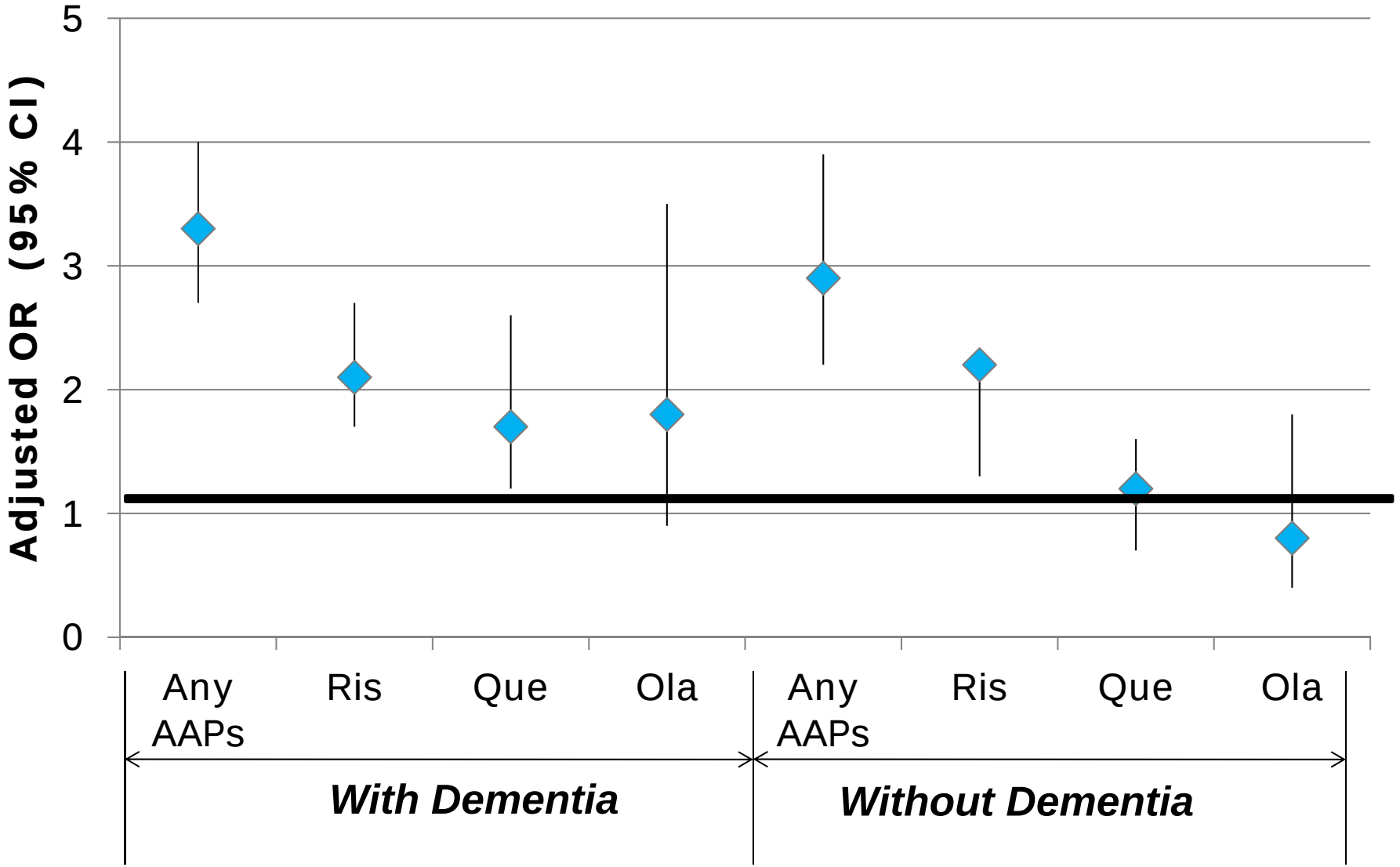
•Adjusted for the use of anticoagulants, other antithrombotic agents, discordant diagnosis of infective endocarditis, valvular heart disease, acute myocardia infarction and atrial fibrillation

Dose-response using Stratified Analysis with DDDs

Exposure in DDDs	N=4803	*Risk window:* 30days aOR* (95% CI)	*Risk window:* 20days aOR* (95% CI)	*Risk window:* *10days* *aOR* (95% CI)*
		Risperidone user		
0	3341	1	1	1
<0.3 DDD	893	3.5(2.9-4.4)	2.3 (1.9-2.9)	1.2 (1.0-1.5)
≥0.3 DDD	569	1.5 (1.2-2.0)	1.9 (1.5-2.5)	1.9 (1.5-2.4)
		Quetiapine user		
0	4216	1	1	
<0.2 DDD	403	2.1(1.5-2.9)	1.3 (1.0-1.8)	0.8 (0.6-1.1)
≥0.2 DDD	184	0.9 (0.5-1.5)	1.1(0.6-1.8)	1.2 (0.7-1.9)
		Olanzapine user		
0	4591	1	1	1
<0.6 DDD	134	0.8 (0.4-1.5)	0.6 (0.3-1.0)	0.3 (0.2-0.5)
≥0.6 DDD	78	0.7 (0.4-1.6)	0.8 (0.4-1.8)	0.8 (0.4-1.8)

•Adjusted for the use of anticoagulants, antiplatelets, other antithrombotic agents, discordant diagnosis of infective endocarditis, valvular heart disease, acute myocardia infarction and atrial fibrillation

Stratified Analysis for the Risk of Ischemic Stroke with and without Dementia



Ris: Risperidone ; Que: Quetiapine ; Ola: Olanzapine

Discussion

- **Increased risk of ischemic stroke associated with AAPs were observed.**
  - **High risk among *risperidone users,* followed by *quetiapine users***

- **Adjusted OR among *olanzapine user* did not show significant risk**
  - **Consistent with previous research**
    (Moretti R et al. 2005; Yulug B et al. 2009)
  - **Dose-response results supports the results.**
  - **Olanzapine might be protective for the risk of ischemic stroke compared to the risperidone, quetiapine.**

Discussion

- **The timing of stroke**
  - ***The highest risk of stroke at one month*** **compared to the risk window** ***longer than one month*** ***(Sacchetti et al. 2009)***
  - **No substantial differences in the results of adjusted OR were observed when assessing the exposure within 30, 20, 10 days before the stroke incidence**
  - ***The results within10 days of risk window only*** **showed dose-response fashion in three type of prescribed AAP drugs.**
    - ***Supports the more detailed information about the timing of stroke.***
    - **This finding suggest the short-term adverse outcome and acute drug effects affecting ischemic stroke incidence.**

- **The dementia as a effect modifier**
  - **Both demented and non-demented patients showed substantially increased risk, however, the risk was higher in demented patients.**

Conclusion

- **AAPs prescription was associated with *increased risk of ischemic stroke .***
  - Particularly among *risperione*, *quetiapine* users
  - Demented patients

- ***Olazapine* might be protective compared to *risperidone*, *quetiapine*.**
  - Need large sample size to confirm the association

- **More careful consideration may be needed to select the type of AAPs for demented elderly patients.**


Thank You!
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