Applications of Pharmacoepidemiology in General Practice

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Outline of content

- **Introduction:** what is Pharmacoepidemiology about?
- **Examples of Automated Databases**
- **Applications of pharmacoepidemiology in GP:**
  - Studying Cause-and-Effect
  - Risk-Association Studies
  - Studies of Drug Utilization
  - Evaluating and Improving Physician Prescription
  - Assessment of Patient Compliance
  - Studies of Medication Errors
- **Future direction of development and promotion**

Pharmacoepidemiology Defined

- The study of **the use of** and **the effects of** drugs in **large numbers** of people – **population level**
- applies the methods of **epidemiology** to the content area of **clinical pharmacology**
  - Epidemiology: **methods** of inquiry
  - Clinical pharmacology: **focus** of inquiry
  - Applies the methods of epidemiology to the content area of clinical pharmacology
- an **effective tool** to **capture useful data** for clinicians, researchers and policy-makers

Pharmaco-vigilance

- the science and activities relating to the **detection, assessment**, **understanding** and **prevention of adverse effects** or any other drug-related problem
- to enhance **patient care and patient safety** in relation to the use of medicines;
- to support **public health programmes** by providing reliable, balanced information for the effective assessment of the **risk-benefit profile** of medicines.

Source: World Health Organization
http://www.who.int/medicines/areas/quality_safety/safety_efficacy/pharmvigi/en/index.html

Examples of Automated Databases

- UK General Practice Research Database
- Group Health Cooperative
- Kaiser Permanente Medical Care Program
- HMO Research Network
- UnitedHealth Group
- Medicaid Databases
- Health Services Databases in Saskatchewan
- Automated Pharmacy Record Linkage in theNetherlands
- Tayside Medicines Monitoring Unit

Types of Databases

- **Administrative database**
  - Collect information for filing claims for payment
- **Medical Records' database**
  - Primary means by which physicians track health information on their patients
- Admin database usually inferior to MR
  - Fail to capture health data (e.g. family history/lifestyle practices)
  - Validity of information lower
- But MR database – still suffer from missing information

UK General Practice Research Database

- The largest medical records database in routine use for epidemiologic investigation
- Used most extensively for published pharmaco-epi research
- Started in 1987
- Based on data routinely recorded by GP using electronic medical records

The Key Success Factors of the UK GPRD

- IN the UK, almost all patient care is coordinated by the GP through the NHS
- For patients referred to specialized care, a Tx plan is formulated by the consultant but chronic therapies are prescribed & monitored by GPs
- Used internationally by researchers from academia, regulatory authorities, and industry

The UKGPRD – Data Collection & Structure

- Provide data on 3 million patient yearly
- Continuous FU data collected for >6 years
- 5% of UK population included
  - Representative (age, sex, residence…)
- An extensive facet of data collected
- Diagnoses (OXMIS) codes until 1995→ ICD-9
- Medication (PPA codes)

Strengths of UK-GPRD

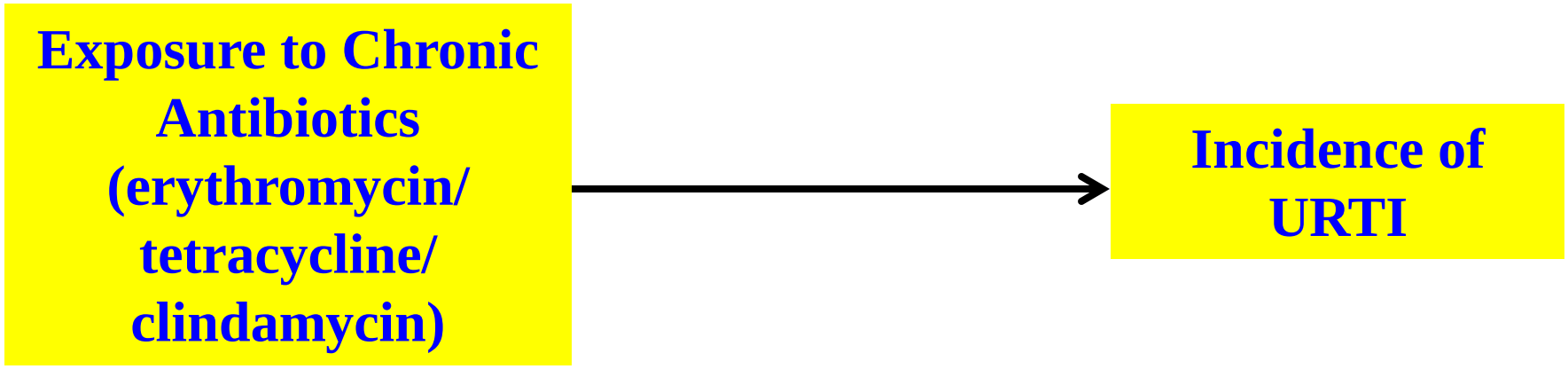
- Population-based data
  - Minimize selection bias; improve validity of epidemiologic studies
- Size of database
  - Cumulative experience 9.8 million patients
  - Over 44.8 million-person years
  - Able to study rare outcomes
- Validity of information
  - Quality of data submitted by GPs under QC

Limitations of UK-GRPD

- **Completeness of dataset**
  - Information from hospitals e.g. test results
- **Complexity & costs of computer software/ hardware needed**
  - Experienced data manager
  - Technically demanding

Example (1):

- **A Research Question**
  - Does chronic (>6 weeks) use of oral or topical antibiotics in acne patients lead to an increased risk of URTI?
  - Which study design shall we use? Are you interested?



Arch Dermatol. 2005;141(9):1132-1136. doi:10.1001/archderm.141.9.1132.

AOR 2.15 (95% C.I. 2.05-2.03)

Exposure to Chronic Antibiotics (erythromycin/ tetracycline/ clindamycin) → **12 months** → **Incidence of URTI**

age, year of diagnosis, sex, practice, history of diabetes, and history of asthma, visit frequency for acne and the no. of prescriptions for acne

Table. Descriptive Variables of Patients With Acne Comparing Those Who Used and Did Not Use an Antibiotic to Treat Their Acne

Variable	No Antibiotic Used (n = 33519)	Antibiotic Used (n = 84977)	*P* Value
Upper respiratory tract infections, No. (%)	3096 (9.2)	15185 (18.6)	<.001
Urinary tract infections, No. (%)	1258 (3.8)	3012 (3.5)	.08
Age, mean (SD), y	21.7 (5.7)	21.4 (5.8)	<.001
Female sex, No. (%)	21507 (64.2)	44725 (52.6)	<.001
Acne-associated office visits, mean (SD)	2.2 (0.01)	2.8 (0.01)	<.001

Arch Dermatol. 2005;141(9):1132-1136. doi:10.1001/archderm.141.9.1132.

Risk-Association Studies

- What is the association between **alarm symptoms** and the **subsequent diagnosis of cancer** in a large population based study in primary care?

- (Question): *What is the resource implication in this study is an RCT design is used?*

Jones et al. Alarm symptoms in early diagnosis of cancer in primary care: cohort study using General Practice Research Database *BMJ2007;334:1040*

The methodology

- 762 325 patients aged ≥15 years between 1994 and 2000
- First occurrences of haematuria, haemoptysis, dysphagia, and rectal bleeding identified in patients with no previous cancer diagnosis

Risk-Association Studies

First onset of haematuria, haemoptysis, dysphagia, or Rectal bleeding

3 years →

Incidence of cancer:
1). Urinary tract Ca
2). Lung Ca
3). Esophageal Ca
4). CRC

- **3-year Positive Predictive Values**:

	Male PPV % (95%C.I.)	Female PPV % (95%C.I.)
Hematuria	7.4% (6.8%-8.1%)	3.4% (2.9%-4.0%)
hemoptysis	7.5% (6.6%-8.5%)	4.3% (3.4%-5.3%)
Dysphagia	5.7% (4.9%-6.7%)	2.4% (1.9%-3.0%)
Rectal bleeding	2.4% (2.1%-2.8%)	2.0% (1.7%-2.3%)

Risk Association Studies

- PPV↑ with age and were strikingly high,
  - men with haemoptysis aged 75-84 (17.1%, 13.5%-21.1%
  - men with dysphagia aged 65-74 (9.0%, 6.8%-11.7%).
- New onset of alarm symptoms:↑cancer Dx, esp in men aged over 65
- provide support for the **early evaluation of alarm symptoms** to identify underlying cancers at an earlier and **more amenable stage**

Studies of drug utilization

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Antihypertensive Medication Use Among US Adults With Hypertension

Qiuping Gu, Ryne Paulose-Ram, Charles Dillon and Vicki Burt

Circulation 2006, 113:213-221: originally published online January 3, 2006
doi: 10.1161/CIRCULATIONAHA.105.542290
Circulation is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0009-7322. Online ISSN: 1524-4539

Figure 1 Antihypertensive drug use among hypertensives aged 18 years by drug class

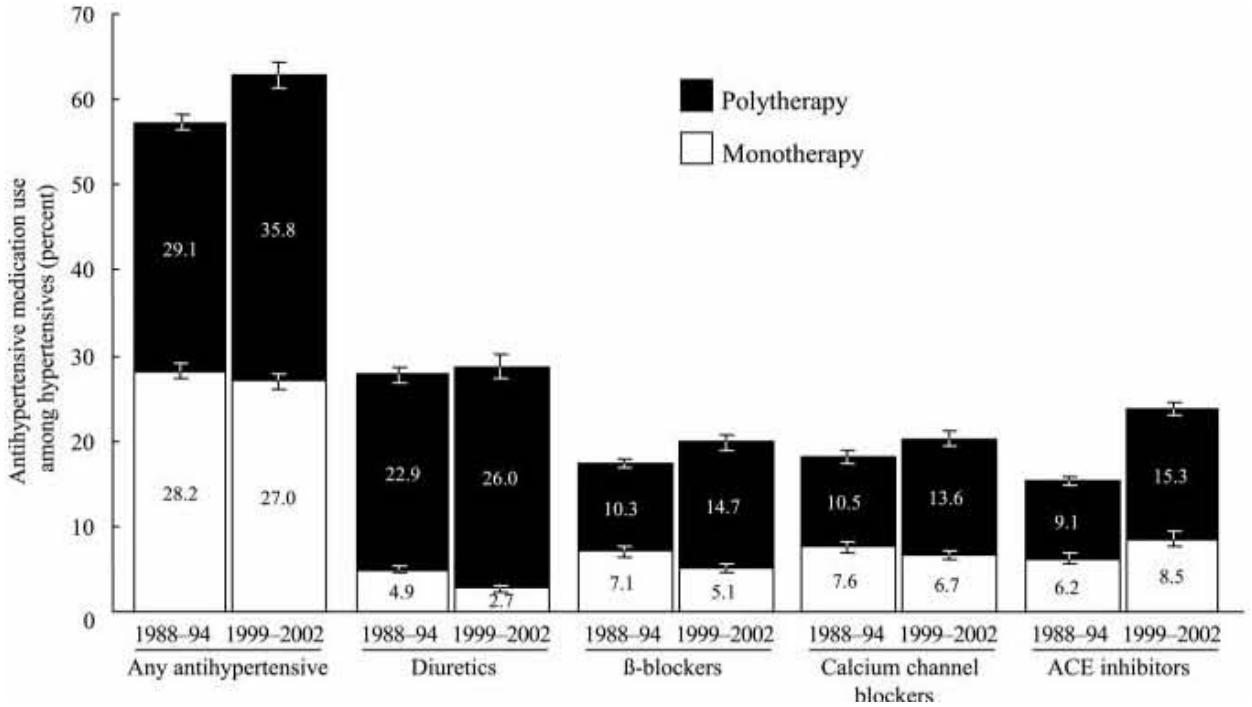

Figure 1. Antihypertensive drug use among hypertensives aged ≥18 years by drug class. Monotherapy indicates use of 1 active ingredient; polytherapy, use of >1 active ingredient. Any antihypertensive includes other antihypertensives and ARBs, not shown separately. Error bars represent SE.

Figure 2. Use of 2 antihypertensive drug

classes among polytherapy users

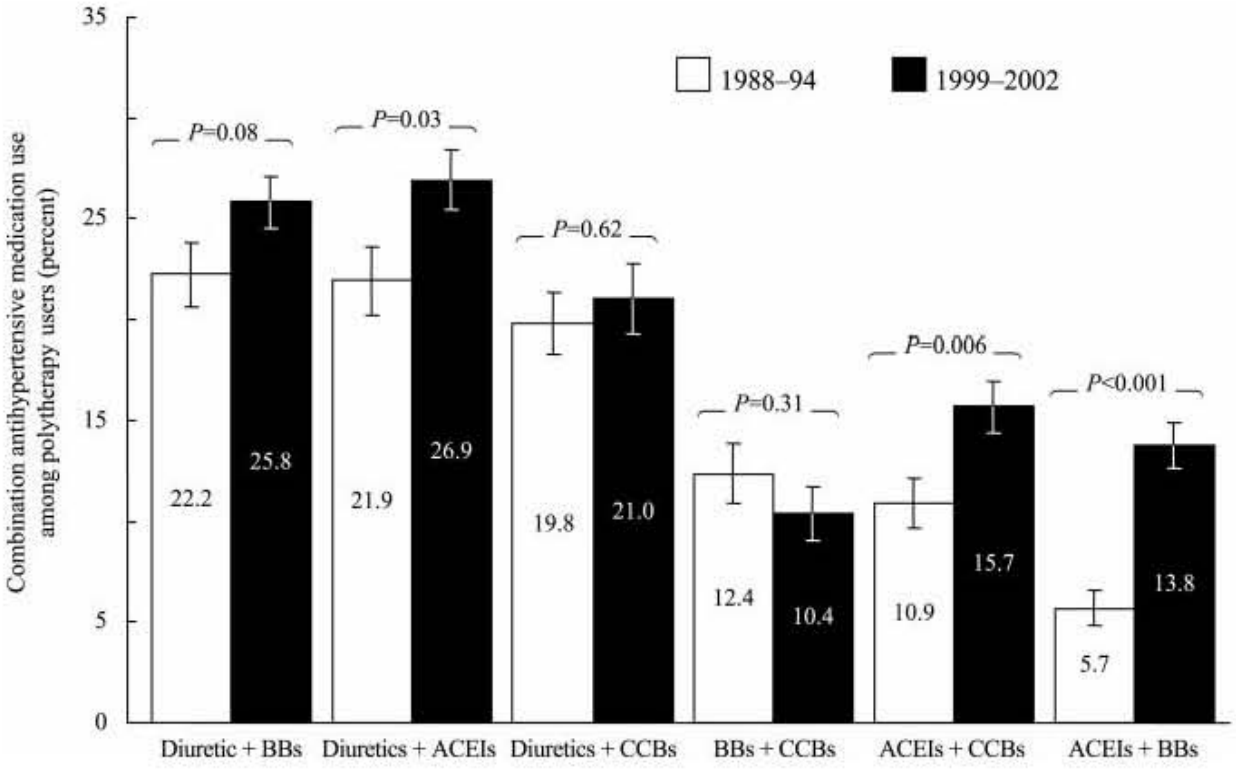

Figure 2. Use of 2 antihypertensive drug classes among polytherapy users. Error bars represent SE. BBs indicates β-blockers; ACEIs, angiotensin-converting enzyme inhibitors. Categories are not mutually exclusive.

Studies of drug prescriptions over time

Hypertension
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Changes in Antihypertensive Prescribing During US Outpatient Visits for Uncomplicated Hypertension Between 1993 and 2004

Jun Ma, Ky-Van Lee and Randall S. Stafford

Hypertension 2006, 48:846-852: originally published online September 18, 2006
doi: 10.1161/01.HYP.0000240931.90917.0c
Hypertension is published by the American Heart Association. 7272 Greenville Avenue, Dallas, TX 72514
 Print ISSN: 0194-911X. Online ISSN: 1524-4563

Figure 1. Trends of prescribing for CCBs (), ACEIs(●), and ARBs (*) as a percent of all hypertension visits in which an antihypertensive drug was reportedly prescribed.

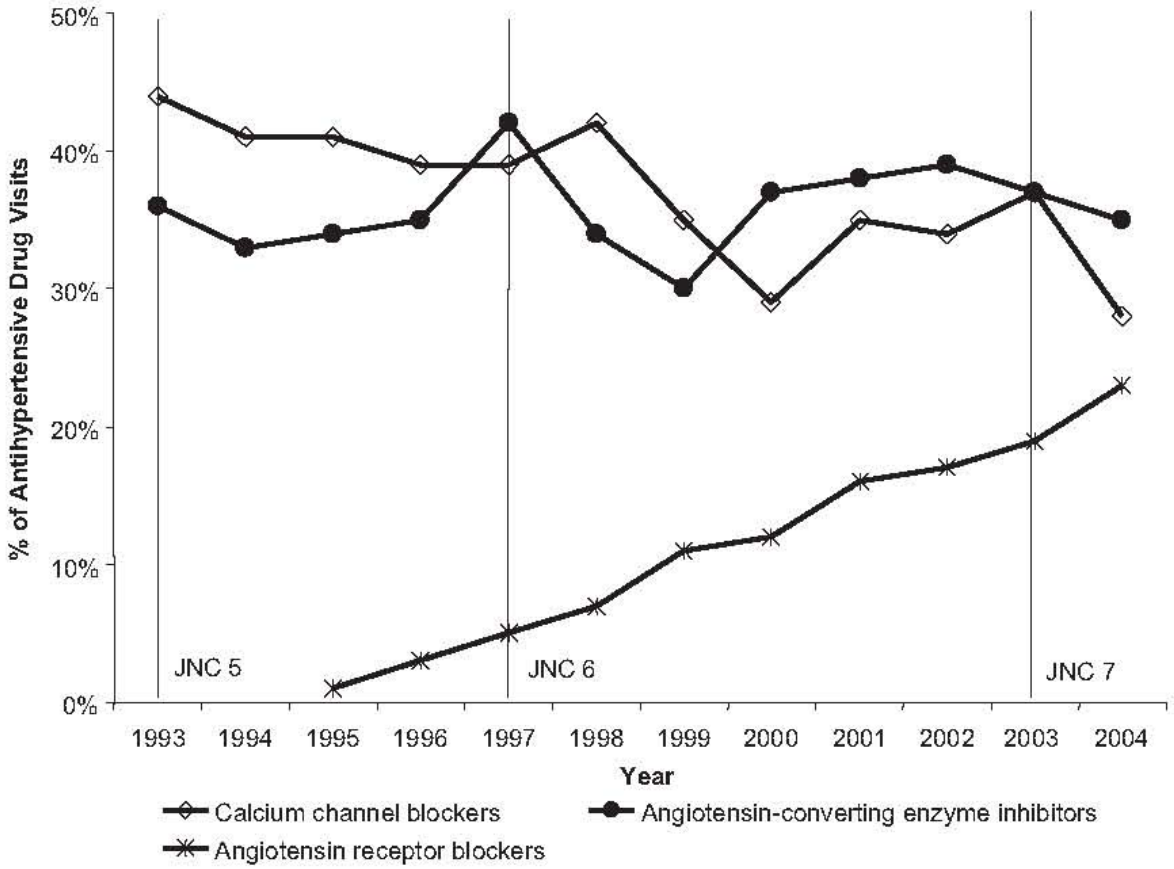

Figure 1. Trends of prescribing for CCBs (◇), ACEIs (●), and ARBs (*) as a percent of all hypertension visits in which an antihypertensive drug was reportedly prescribed.

Figure 2. Trends of prescribing for diuretics & β-blockers as % of all hypertension visits in which an antihypertensive drug was reported prescribed.

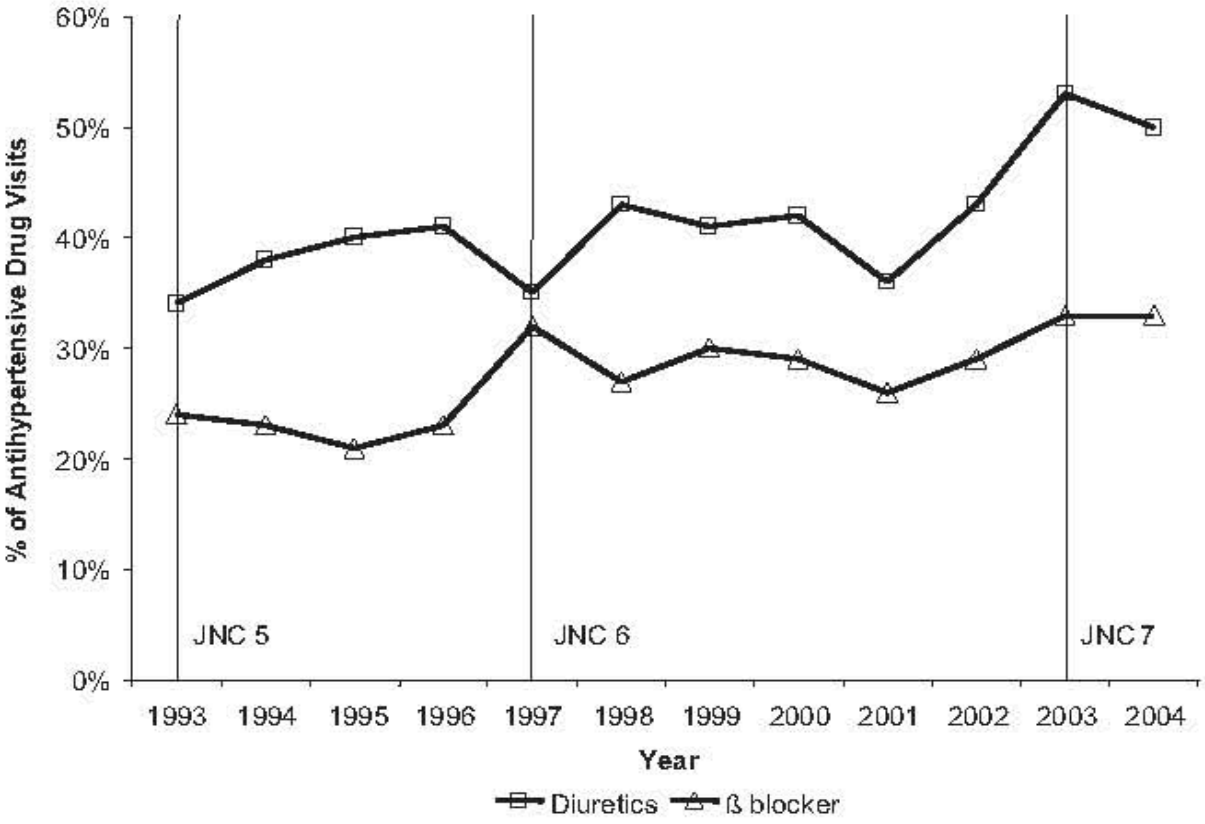

Figure 2. Trends of prescribing for diuretics (□) and β-blockers (Δ) as a percent of all hypertension visits in which an antihypertensive drug was reported prescribed.

Some arguments of the need for pharmacoepidemiology studies

- Becoming more important to reflect "real life clinical practice" on pharmacological effects of medications and their utilization

- What happened to the RCTs?
  - Are they not robust enough?

European Heart Journal (2007) **28**, 1462–1536
doi:10.1093/eurheartj/ehm236

2007 Guidelines for the management of arterial hypertension

The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC)

Authors/Task Force Members: Giuseppe Mancia, Co-Chairperson (Italy), Guy De Backer, Co-Chairperson (Belgium), Anna Dominiczak (UK), Renata Cifkova (Czech Republic) Robert Fagard (Belgium), Giuseppe Germano (Italy), Guido Grassi (Italy), Anthony M. Heagerty (UK), Sverre E. Kjeldsen (Norway), Stephane Laurent (France), Krzysztof Narkiewicz (Poland), Luis Ruilope (Spain), Andrzej Rynkiewicz (Poland), Roland E. Schmieder (Germany), Harry A.J. Struijker Boudier (Netherlands), Alberto Zanchetti (Italy)

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ESH Scientific Council: Sverre E. Kjeldsen, President (Norway), Serap Erdine, Vice-President (Turkey), Krzysztof Narkiewicz, Secretary (Poland), Wolfgang Kiowski, Treasurer (Switzerland), Enrico Agabiti-Rosei (Italy), Ettore Ambrosioni (Italy), Renata Cifkova (Czech Republic), Anna Dominiczak (United Kingdom), Robert Fagard (Belgium), Anthony M. Heagerty, Stephane Laurent (France), Lars H. Lindholm (Sweden), Giuseppe Mancia (Italy), Athanasios Manolis (Greece), Peter M. Nilsson (Sweden), Josep Redon (Spain), Roland E. Schmieder (Germany), Harry A.J. Struijker-Boudier (The Netherlands), Margus Viigimaa (Estonia)

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The affiliations of Task Force members are listed in the Appendix. Their Disclosure forms are available on the respective society Web Sites. These guidelines also appear in the *Journal of Hypertension*, doi:10.1097/HJH.0b013e3281fc975a

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4. Evidence for therapeutic management of hypertension

4.1 Introduction

Recommendations about therapy for hypertension are here preceded by some considerations on the strength of available evidence on the benefits associated with antihypertensive treatment as well as on the comparative benefits of the various classes of drugs. There is a consensus that large randomized trials measuring fatal and non-fatal events represent the strongest type of evidence available. However, it is commonly recognized that event based randomized therapeutic trials also have limitations.[3,273,274]

These include the need to select elderly or otherwise high risk patients in order to maximize the number of events collected and thus the power of trials, which means that uncomplicated, younger and lower risk patients are rarely represented, with the unfortunate consequence that little direct information is available on treatment benefits in a large sector of the hypertensive population. Furthermore, the therapeutic programmes of trials often diverge from usual therapeutic practice because drugs randomly allocated at the beginning of a trial are continued even in absence of blood pressure lowering effects, while in practice physicians normally do not continue prescribing drugs that are not effective; therefore in trials, but not in practice, benefits occurring in subjects responsive to the allocated treatment are diluted by the lack of benefit in non-responsive subjects.

Perhaps the most important limitation is the necessarily short duration of a trial (in most cases 4 to 5 years) whereas additional life expectancy, and hence expectancy of treatment duration, for middle age hypertensives is 20 to 30 years. Long term therapeutic benefits, as well as differences in benefit between various drug classes, have recently been investigated by prolonging the observation of patients after the end of trials,[275,276] but this can only be done in an uncontrolled fashion, which limits the value of the results.

- These include the need to select elderly or otherwise high risk patients in order to maximize the number of events collected and thus the power of trials, which means that uncomplicated, younger and lower risk patients are rarely represented, with the unfortunate consequence that little direct information is available on treatment benefits in a large sector of the hypertensive population. Furthermore, the therapeutic programmes of trials often diverge from usual therapeutic practice because drugs randomly allocated at the beginning of a trial are continued even in absence of blood pressure lowering effects, while in practice physicians normally do not continue prescribing drugs that are not effective; therefore in trials, but not in practice, benefits occurring in subjects responsive to the allocated treatment are diluted by the lack of benefit in non-responsive subjects.

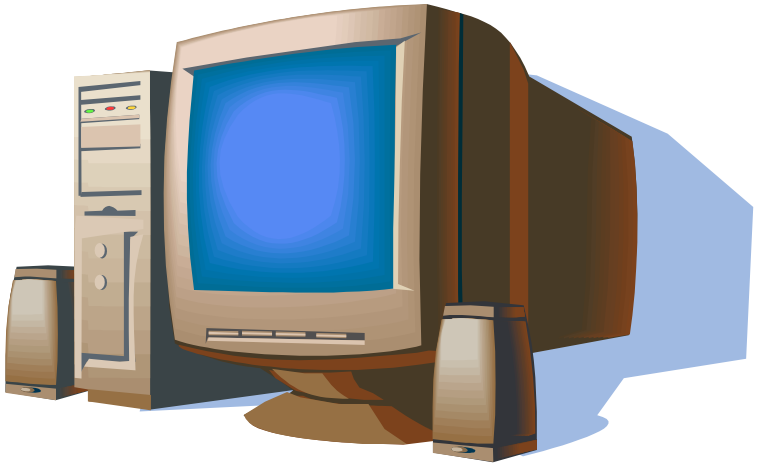
- Perhaps the most important limitation is the necessarily short duration of a trial (in most cases 4 to 5 years) ……

2007 Guidelines for the management of arterial HT

- 1) the need to select higher risk patients
- 2) uncomplicated, younger and lower risk patients were under-represented
- 3) not representing real clinical practice
- 4) Prolonging the observation of patients after the end of trials might capture more “real-life” outcomes but these can only be done in an uncontrolled manner,
  - the problem of selection bias still exist.

References: The Task Force for the Management of Arterial Hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC), 2007 Guidelines for the management of arterial Hypertension. Eur Heart J (2007) 28 (12): 1462-1536.

- **An Example of Establishing a local Hong Kong-wide database to perform Pharmaco-epidemiology studies…**



Proven effectiveness of antihypertensive therapies

- **↓ the incidence of**
  - heart failure by 50%,
  - stroke by 40–45%, and
  - myocardial infarction by 20–25%
- **In trial settings**

References:
1. Chobanian et al. The seventh report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of high blood pressure: The JNC 7 report. JAMA. 2003;289:2560–2572.
2. Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials.*Lancet.* 2003;362:1527–1535.

Suboptimal compliance

- ↓ persistence with prescriptions with time esp. in the 1st year of treatment
- **Consequences:**
  - ↑ Morbidity rates,
  - ↑ Mortality,
  - ↑ Hospitalization rates and healthcare costs

References:
1. Sokol, M.C., et al. Impact of medication adherence on hospitalization risk and healthcare cost. Med. Care 2005;43:521–530.
2. Hughes, D.A., et alThe impact of non-compliance on the cost-effectiveness of pharmaceuticals: a review of the literature. Health Econ. 2001; 10:601–615.

Circulation
JOURNAL OF THE AMERICAN HEART ASSOCIATION

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Adherence to Antihypertensive Medications and Cardiovascular Morbidity Among Newly Diagnosed Hypertensive Patients

Giampiero Mazzaglia, Ettore Ambrosioni, Marianna Alacqua, Alessandro Filippi, Emiliano Sessa, Vincenzo Immordino, Claudio Borghi, Ovidio Brignoli, Achille P. Caputi, Claudio Cricelli and Lorenzo G. Mantovani

Circulation. 2009;120:1598-1605; originally published online October 5, 2009;
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

- ↑ antihypertensive adherence associated with ↓ risk of acute CVS events (**hazard ratio 0.62**, 95% C.I. 0.40–0.96)

Circulation
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American Heart Association®

Impact of Nonadherence to Antihypertensive Therapy

Aram V. Chobanian

Circulation. 2009;120:1558-1560; originally published online October 5, 2009;
doi: 10.1161/CIRCULATIONAHA.109.906164
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- Important to investigate this in greater depth & in real-life setting
- One of the major determinants of compliance
  - the **patients' race and ethnicity** → introduces

Objectives

- to test the ***a priori*** hypothesis that better medication adherence leads to lower mortality from CHD and stroke in a large Chinese population

- Retrieval of data from clinical databases

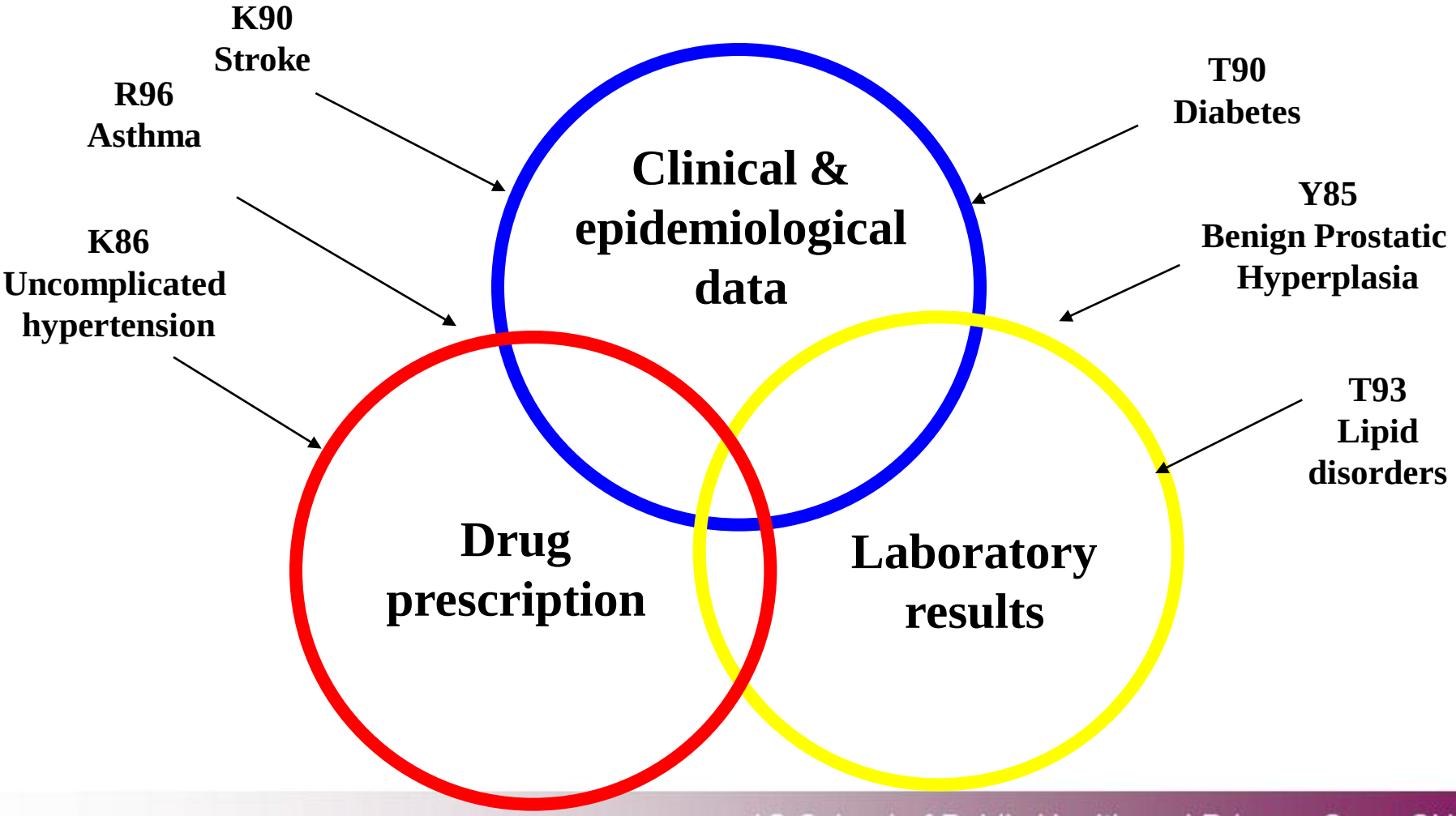
Methods

- **Data Source**
  - CDARS & CMS, Hospital Authority
  - included all Hong Kong residents > 7 million
  - Robustness of database evaluated
    - High completeness of demographic data (100%) & prescription details (99.98%)

*Wong MCS, Jiang Y, Tang JL, Lam A, Fung H, Mercer SW, Griffiths S. Health services research in the public healthcare system in Hong Kong: An analysis of over 1 million antihypertensive prescriptions between 2004-2007 as an example of the potential and pitfalls of using routinely collected electronic patient data. *BMC Health Services Research* 2008;**8**:138

Construction of a "clinical research database"

ICPC-2: International Classification of Primary Care;
ICD-9: International Classification of Disease



The Database: its robustness for research purpose

- **sole portal for information** used in all public clinical settings
- allows **linkage of information** when patients visit clinics in different districts
- All physician prescriptions **checked by dispensers or pharmacists** using standardized procedures
- any **amendments** in the prescriptions were captured in the database

Participants

- **Patients who**
  - attended any consultations in the public sector and
  - who were prescribed their first-ever antihypertensive medications between 2001 to 2005 (the index date)
    - excluded patients who were prescribed any antihypertensive drugs before the index date
  - each patient was allocated **according to the initial prescription of antihypertensive drugs**, namely, α-blockers, β-blockers, thiazide diuretics, CCB and ACEIs

Outcomes & Predictors

- **Mortality** due to coronary heart disease (ICD-9 I20 to I25.1) and cerebrovascular disease (ICD-9 I60–I66.9).
  - the vast majority of deaths occurred in hospitals in HK
  - accurate case ascertainment

- **Predictor: interval-based PDC**
  - (the no. of days when Px. is supplied in a specified period) ÷ (the total number of days within the period)
  - internationally accepted metric
  - PDC $\geq$ 80%: high medication-adherent;
  - PDC 40-79%: intermediate;
  - PDC<40%: low

Covariates

- Patients' Age
- Gender
- Fee payment status
- Region of residence (deprivation index)
- Type of clinic visits
- No. of concomitant comorbidities,
  - "DM or IGT" (23.0%), "CVS" (24.3%), "Respiratory diseases" (14.6%) and "Renal diseases" (11.0%).
- Levels of SBP and DBP averaged over all clinic visits
- Initial anti-HT drug class

Statistical Analysis

- Cox Proportional Hazard model

- Y (**CVS deaths**) = x1 (**interval-based PDC**) + x2 (age) + x3 (gender) + …+ ε

- Additional analysis: adjusted estimates weighted by the inverse estimated **propensity scores** → control treatment indication bias

Results

- **218,047** eligible subjects
- 3,825 patients (1.75%) died of CVS ≤ 5 years

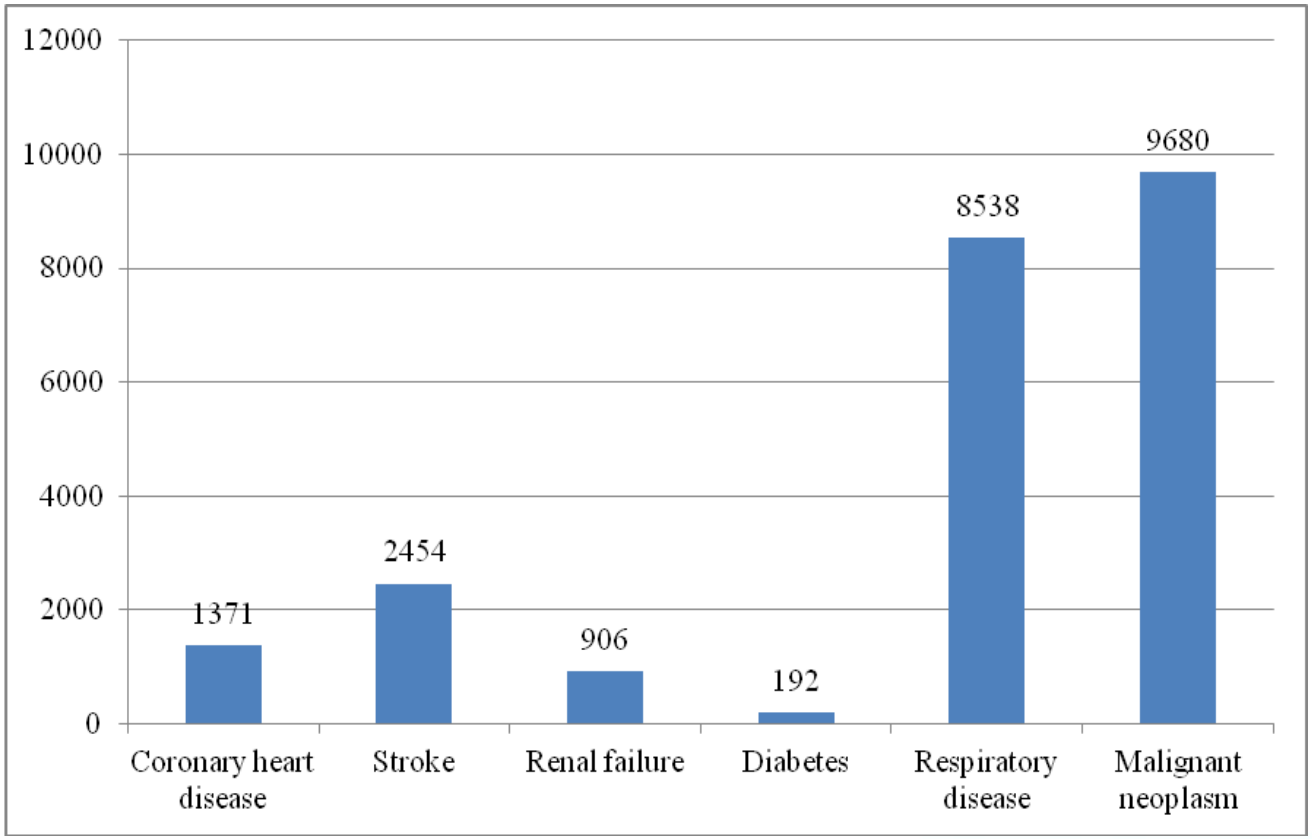


Table 1 Baseline Characteristics of Patients (N=218,047)

	N*	%	p
Proportion Days Covered in 5 years' follow-up			
<40%	71,734	32.9	<0.001
40-79%	26,478	12.1	
≥ 80%	119,834	55.0	
Gender			
Male	98,270	45.1	<0.001
Female	119,775	54.9	
Age			
<50	61,362	28.1	<0.001
50-59	42,027	19.3	
60-69	41,627	19.1	
≥ 70	73,011	33.5	

Table 3 Association between medication persistence and cardiovascular mortality 5 years within cohort entry

	Hazard ratio (95% C.I.)	p
Age		
<50	1.00 (reference)	<0.001
50-59	2.28 (1.83-2.84)	
60-69	5.65 (4.67-6.83)	
≥ 70	15.79 (13.24-18.82)	
Gender		
Male	1.00 (reference)	<0.001
Female	0.79 (0.74-0.85)	
Public assistance		
No	1.00 (reference)	<0.001
Yes	1.15 (1.07-1.24)	
Proportion of Days Covered (PDC) at 6 months		
<40%	1.00 (reference)	
40-79%	**0.46 (0.41-0.52)**	**<0.001**
≥ 80%	**0.91 (0.85-0.98)**	**0.012**
First Prescription		
Thiazide diuretics	1.00 (reference)	
ACEIs	1.31 (1.13, 1.52)	<0.001
β-blockers	1.02 (0.89-1.18)	0.738
CCBs	1.21 (1.06-1.38)	0.005

- **Patients with higher PDC** had lower hazards of mortality
- **ACEI & CCB receivers** had higher hazards of mortality

Discussions

- The largest observational study among Chinese patients showing **better compliance leads to lower mortality** in **real-life settings**.

- The finding that the prescriptions of ACEIs and CCBs were associated with higher CVS mortality
  - ACEI/CCBs more commonly prescribed in patients with concomitant comorbidities

Limitations

- Database assumptions
- Capture only patients seen in the public sector
- Not all confounders are controlled – residual confounding
- Treatment indication bias despite the use of propensity scores - Sicker patients adhere better??

Implications to clinical practice

- Strengthened the notion that ↑ medication adherence would protect against cardiovascular mortality in interventional settings & also in actual clinical practice
- more concrete evidence to support more intensive counselling on medication adherence
- At a health-policy level, a greater need for community-based programmes and strategies to enhance compliance

Future research…

- Evaluate this association in other ethnic groups &in patients with different CVS risks
- Identify patient subgroups where the impact of enhancing medication adherence is the strongest
- Strengthen the use of medication adherence as an outcome variable on proxy of CVS outcomes

Future direction of development

- **1) Rapid development & increased interests globally**
- Annual international conference on pharmacoepidemiology: attendance 50 (1980) → 900 (2004)
- ISPE: 800 members from 37 countries; guidelines (2004)

  Academic Journals: *Clin Pharmacol Ther. (IF: 6.961, 11/237); J Clin Epidemiol; Pharmacoepidemiol & Drug Saf.*
  - Actively solicit pharmaco-epi studies
- ↑ number of summer programmes on pharmaco-epidemiology
  - Michigan SPH (10%), McGill, Erasmus U. Rotterdam, Johns Hopkins
- Initiatives from pharmaceutical companies
  - Forming their own pharmaco-epidemiology units

Future direction of development

- **2) The academics**
- **Methodologic advances**
  - Expanded use of neural networks, propensity scores, sensitivity analyses, time-varying exposures & confounder control, data mining
  - Involvement of pharmacoepidemiologists into policy questions
  - Emergence of pharmacogenetic studies
- **New content areas of interest**
  - E.g. drug utilization, prescription profiles
- **Logistical advances**
- **Funding & Personnel**

Future direction of development

- **2) The academics**
- **Training in statistical techniques**
  - Confounding management
  - Use of propensity scores
- **Better use of large-scale datasets**
  - Coding rate of HT (ICPC-2 K86)/ DM (ICPC-2 T90)
  - Coding rate is increasing

Future direction of development

- **3) The Industry – role of pharmacoepi expanding**
  - Contribute to identify problems & document drug safety
  - Develop & evaluate risk management programme
  - "Prophylactic" studies by manufacturers
  - Post-marketing studies for all newly marketed drugs for chronic diseases
  - Protect major investment made in developing a new drug
    - Reduce legal liability
- Pharmaceutical companies: ↑ investment in external pharmacoepidemiologic data resources
  - Need adequately trained researchers with statistical skills & robust dataset

Future direction of development

- **4) The Regulatory Agencies**
- Also expanding
- Postmarketing pharmaco-epi studies replacing pre-marketing phase III studies (e.g. zidovudine)
- Use of therapeutic risk management approaches – change regulation
- Increase attention to drug safety (COX-2 inhibitors; NSAIDs)

Future direction of development

- **5) The Law**

- ↑ No. of lawsuits related to adverse drug effects

- ↑ Awareness of the legal system's ability to obtain substantial remuneration for those suffered from adverse effects

- Financial payments: put entire drug company at risk

References

Pharmacoepidemiology / edited by Brian L. Strom.
Chichester ; Hoboken, NJ : J. Wiley, c2005.
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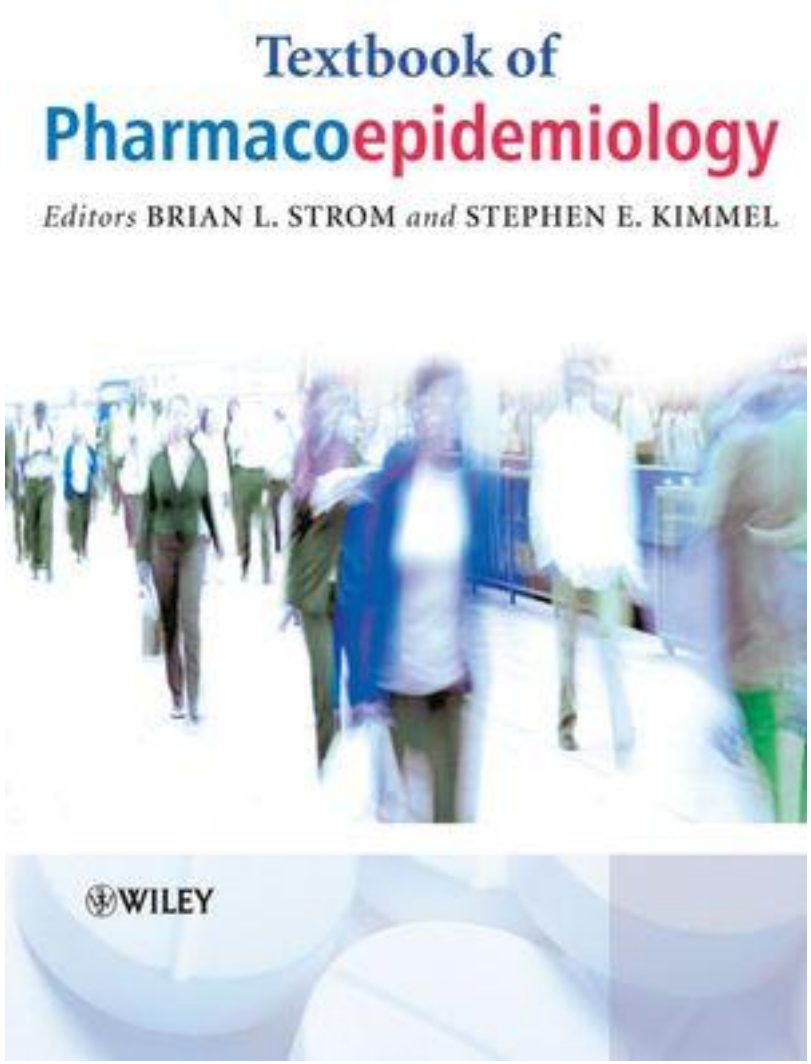

Future direction of development

- Let’s join our hands …
- Thank you !!