Australian Government
Department of Health
Therapeutic Goods Administration

Linked Administrative Data for Pharmacovigilance: *Direct-acting oral anticoagulants and intracranial haemorrhage*

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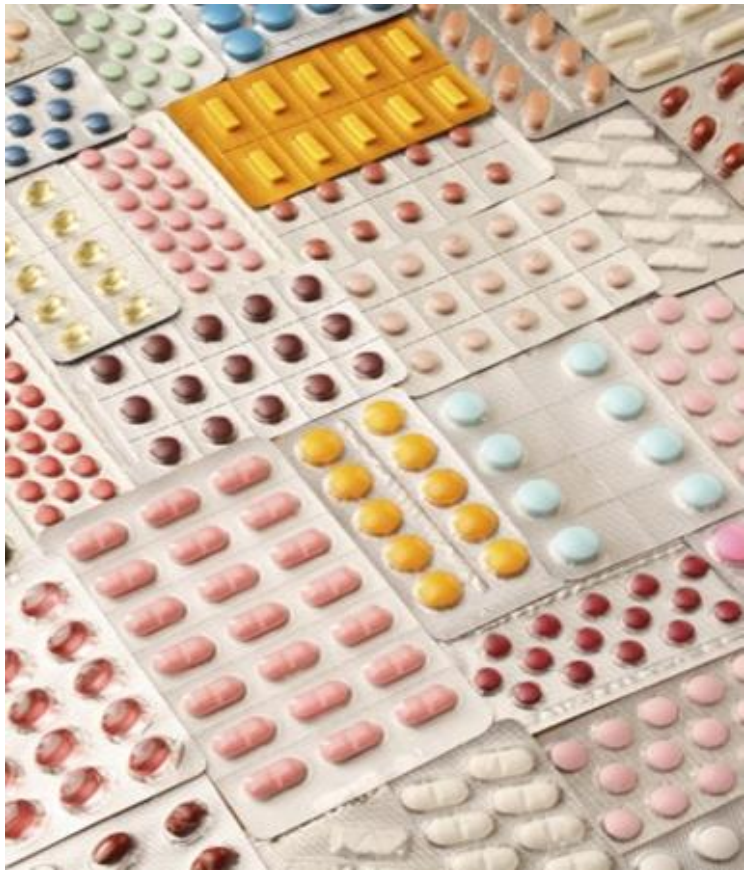
RACP Congress 2019 - Gerry Murphy Presentation

TGA Health Safety Regulation

Background

- Clinical trials have limitations in their ability to detect safety issues for new medicines.
- Spontaneous reporting system for adverse events are subject to significant underreporting.
- Population-level health data is increasingly being used to investigate safety signals for medicines.



Background

- **Requirements for suitable research question**

  - Identification of medicine exposure and outcome in available datasets
  - Sufficient number of exposed study participants to achieve adequate power
  - Issues with identifying known confounders within available datasets

Background

- Clinical trials showed lower rates of bleeding for dabigatran compared with warfarin
- Large number of adverse drug reaction (ADR) reports for bleeding from various sites post registration
  - Southworth MR, Reichman ME, Unger EF. Dabigatran and postmarket reports of bleeding. *NEJM* 2013; 268(14): 1272-1274.

- Is this a reporting bias for new medicines, or are bleeding rates higher in non-trial settings?

Aim and objectives

- This project aimed to assess the feasibility of using linked administrative health data to enhance current pharmacovigilance methods, using the Sax Institute's 45 and Up study.

- Objective:
  - Investigate the association between specific drugs and adverse drug reactions within linked 45 and Up study datasets.

Direct acting oral anticoagulants vs warfarin

and

Intracranial haemorrhage

This project receives institutional oversight from the NSW Population and Health Services Research Ethics Committee and the ACT Health Human Research Ethics Committee.

The Sax Institute 45 and Up study funding partners are Cancer Council NSW, National Heart Foundation of Australia (NSW division), NSW Ministry of Health, NSW Government Family and Community Services – Ageing, Carers and the Disability Council NSW, and the Australian Red Cross Blood Service.

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Methods

Sax Institute 45 and Up Study

- Ongoing, longitudinal study of NSW residents aged 45 years and over
- Cohort size N=267,153
- Probabilistic data linkage of survey and administrative datasets undertaken by the NSW Centre for Health Records Linkage (CHeReL).

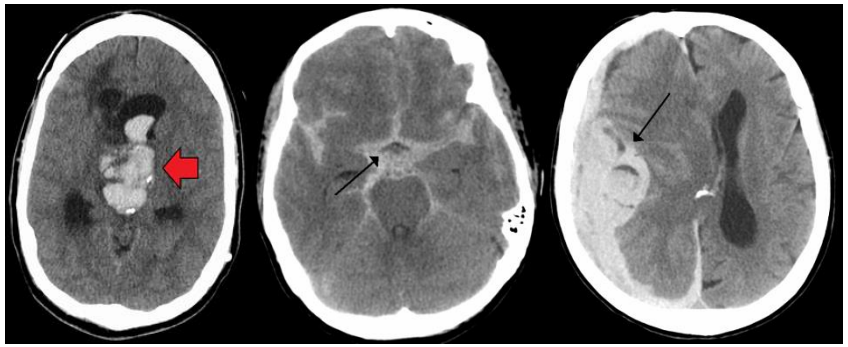
- Further information:
  - 45 and Up Study Collaborators. Cohort Profile: The 45 and Up Study. *Int J Epid*. 2008;37(5):941-947.
  - https://www.saxinstitute.org.au/our-work/45-up-study/

Methods

Direct-acting oral anticoagulants and intracranial haemorrhage

- Incident user, cohort study

- Study population – participants with **PBS concessional status**
  - **Exposure** – apixaban, rivaroxaban or dabigatran users
  - **Comparator** – warfarin users
  - **Exclusions** – PMHx mechanical heart valve, mitral stenosis, severe renal impairment
  - **Outcomes** – intracranial haemorrhage, mortality
  - **Observation period** - January 2009 to December 2015; Index date at first target-medicine dispensing



Methods

- **Statistical analysis**
  - Cox proportional hazards and marginal structural modelling
  - Weighting by propensity score and inverse probability of treatment
  - Combined and individual models for DOACs

  - Sensitivity analysis:
    - Limit indication of use to non-valvular atrial fibrillation using hospital discharge information

Results

	DOAC users	Warfarin users	Total
Sample size (% of total sample)	4,316 (38%)	6,976 (62%)	11,292
Number of participants with an ICH-related hospitalisation or death record (% of treatment group)	11 (0.3%)	72 (1.0%)	83
Number of participants with an all-cause death record (% of treatment group)	75 (1.5%)	536 (7.7%)	611
Male	45.3%	51.5%	p<0.001
Mean age	71.1%	72.8%	p<0.001
Previous history ICH	0.5%	0.9%	p<0.02
Coprescribed antiplatelet	4.1%	8.9%	p<0.0001

Results

Model	Sample size by exposure group		Hazard ratio, 95% CI	P value
	DOAC	Warfarin		
Combined DOAC	4316	6976	0.61, [0.46, 0.80]	0.0003
Dabigatran	484	6976	0.52, [0.27, 0.98]	0.04
Rivaroxaban	2825	6976	0.51, [0.37, 0.72]	<0.0001
Apixaban	1007	6976	0.56, [0.35, 0.90]	0.02
Users with AF/dabigatran	218	2500	0.43, [0.18, 1.05]	0.07
Users with AF/rivaroxaban	551	2500	0.64, [0.39, 1.05]	0.08
Users with AF/apixaban	480	2500	1.01, [0.62, 1.64]	0.1

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Discussion

- Findings consistent with other studies utilising similar methodologies in different jurisdictions (US[1], NZ[2]), indicating a **lower risk of intracranial haemorrhage for DOACs compared with warfarin**.

  - Significantly lower rate of ICH in DOAC users than that reported in clinical trials[3]
    - Study participants hospitalised or dying in other jurisdictions
    - Poorer compliance with treatment in real-world setting
    - Incomplete outcome measurement

[1]Graham DJ, et al. Circulation. 2015; 131: 157-164.

[2]Nishtala PS, et al. Int J Cardiol. 2016; 203: 746-752.

[3]VHA Pharmacy Benefits Management Services. Medical Advisory Panel and VISN Pharmacist Executives. Drug Class Review: Target Specific Oral Anticoagulants Dabigatran (Pradaxa), Rivaroxaban (Xarelto), and Apixaban (Eliquis). 2014.

Strengths

Rich data source

Large sample size

“Real world” medicine use

Limitations

Observational

Healthy participant bias

Choice of medicine and ADR

Lack of info on prescribing indication

Lack of primary care data

Significance for public health

Harm from medicines is a serious threat to public health

Pharmacovigilance aims to prevent and reduce harms associated with medicine use

Need for real-world data

Comparative effectiveness

Increased capacity within TGA for future research

Conclusion

Use of linked administrative datasets for pharmacovigilance is feasible

Choice of research question is crucial

Acknowledgements

- Project team
- Sax Institute
- Participants of the 45 and Up study

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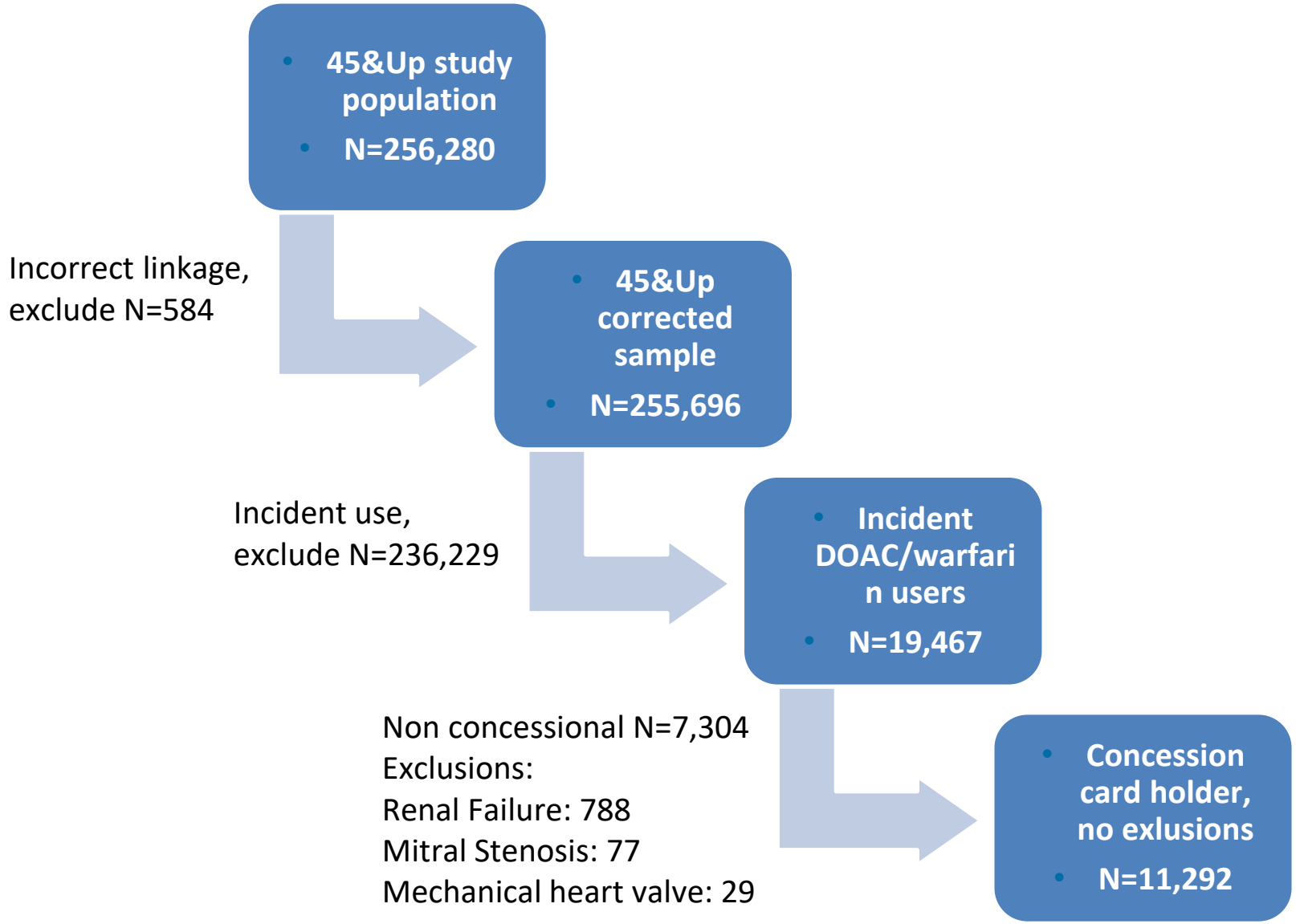
Results


45&Up study population
N=256,280
Incorrect linkage, exclude N=584
45&Up corrected sample
N=255,696
Incident use, exclude N=236,229
Incident DOAC/warfarin users
N=19,467
Non concessional N=7,304
Exclusions:
Renal Failure: 788
Mitral Stenosis: 77
Mechanical heart valve: 29
Concession card holder, no exlusions
N=11,292