Characteristics of selective and non-selective NSAID use in Scotland

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Cardiovascular Safety

VIGOR (2000)[1]	CLASS (2000)[2]
To assess whether rofecoxib was associated with lower incidence of clinically important upper GI adverse events compared to naproxen	To assess whether Celecoxib was associated with lower incidence of upper GI ulcer complications compared to diclofenac sodium & ibuprofen.
Aspirin users excluded	20% of patients in each group were aspirin users.
Rate of upper GI adverse events: • 2% for rofecoxib; 4% for naproxen	Rate of upper GI ulcer complications: • All patients: 0.76% for celecoxib, 1.45% for other NSAIDs (P=0.09) • Patients not taking aspirin: 0.44% for celecoxib, 1.27% for other NSAIDs (P=0.04) • Patients taking aspirin: 2.01% for celecoxib, 2.12% for other NSAIDs (P=0.92) RR of an upper GI ulcer complication was 4.5 with concomitant aspirin use for celecoxib users.
Rate of MIs: 0.4% for rofecoxib; 0.1% for naproxen	Incidence of cardiovascular events similar in both groups

1. Bombardier C, *et al*., (2000). Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Eng J Med*, **343**:1520-1528.
2. Silverstein FE, *et al*., (2000). Gastrointestinal toxicity with Celecoxib vs. nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS Study: A Randomised Controlled Trial. *JAMA*, **284** (10):1247-1255.

Vioxx Market Withdrawal

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Daily Mail, Friday, October 1, 2004

V1

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Arthritis drug used by 400,000 withdrawn

A DRUG used by hundreds of thousands of arthritis sufferers was pulled off the market yesterday amid fears it raises the risk of heart attack and stroke.

Researchers found that patients taking the painkiller Vioxx for 18 months had double the risk of cardiovascular problems compared with those taking a 'dummy' pill.

The U.S. manufacturer, Merck Sharp & Dohme, stopped the research and withdrew the drug. The move wiped $25billion off its share value.

U.S. experts say the findings raise questions over arthritis drugs known as COX-2 inhibitors.

They are used in the treatment of pain and inflammation in osteoarthritis and rheumatoid arthritis, and in the management of acute pain.

Dr Garret FitzGerald, of Pennsylvania University, said: 'This has implications for all members of this class.'

About 400,000 British patients are taking Vioxx, which was marketed as having fewer damaging side effects than conventional medication.

The Government's Medicines and Healthcare Products Regulatory Agency said patients taking Vioxx, or

By **Jenny Hope**
Medical Correspondent

rofecoxib, should contact their doctor for alternative treatment.

Concerns were first raised two years ago that Vioxx might cause heart attacks, with clinical trials suggesting the drug increased the incidence of blood clots tied to strokes and heart attacks.

The new evidence comes from a three-year study of 2,600 patients to discover whether using the drug at a 25mg dose would protect against colon cancer. But the trial was halted after Merck discovered patients taking Vioxx had a higher heart attack risk.

Dr Mayur Lakhani, of the Royal College of General Practitioners, said: 'There is no cause for alarm, but if people are worried we would advise them to stop taking Vioxx and use a safer painkiller, which their local pharmacist will be able to advise them on.'

Worldwide sales of Vioxx, which was launched in 1999, were $2.5billion (£1.4billion) last year.

In a statement, Merck's chairman Raymond Gilmartin said: 'We are taking this action because we believe it best serves the interests of patients.

'Although we believe it would have been possible to continue to market Vioxx with labelling that would incorporate these new data, given the availability of alternative therapies, and the questions raised by the data, we concluded that a voluntary withdrawal is the responsible course to take.'

■ *The charity Arthritis Care runs a helpline on 0808 800 4050*

Adematous Polyp Prevention on Vioxx (APPROVe) Trial[3,4]

- Prospective, randomised, placebo-controlled, double-blind clinical trial
- to determine the effect of long-term treatment with rofecoxib on recurrence of colorectal polyps in patients with a history of colorectal adenoma
- 2,600 patients enrolled
- compared treatment with rofecoxib with placebo over 3 years
- Absolute serious thrombotic event rate for:

  Placebo - 3 per 400 patient years

  Rofecoxib (25mg daily) - 6 per 400 patient years
- beginning after 18 months of continuous use of rofecoxib

3. Anonymous.http://www.vioxx.com/rofecoxib/vioxx/consumer/index.jsp [Accessed October 2004]
4. Anonymous. http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/vioxx.htm [Accessed October 2004]

Adenoma Prevention with Celecoxib (APC) Trial[5]

- Compared celecoxib with placebo for reducing the risk of colon polyps.
- Over 2000 patients enrolled with 33 months being the average duration of treatment
- Interim analysis showed that patients taking:
- 400mg celecoxib x2 daily ⟹ 3.4 times greater risk of CV events compared to placebo.
- 200mg celecoxib x2 daily ⟹ 2.5 times greater risk of CV events compared to placebo.
- National Institute of Health Sciences announced the suspension of use of celecoxib in the ongoing trial on 17th December 2004.

5. Anonymous. http://www.nih.gov/news/pr/dec2004/od-17.htm

Impact of APPROVe trial & APC trial

- Medicines & Healthcare products Regulatory Agency (MHRA) advice for prescribers[6]:
  - 'Patients treated with any COX-2 inhibitor who have established ischaemic heart disease or cerebrovascular disease should be switched to alternative (non-COX-2 selective) treatments as soon as is convenient.'
  - 'For all patients, alternative treatments should be considered in light of an individual assessment of risks and benefits of COX-2 inhibitors, in particular cardiovascular, gastrointestinal and other risk factors.'

6. Anonymous. http://medicines.mhra.gov.uk/ourwork/monitorsafequalmed/safetymessages/celecoxibhealthlink201204doc.pdf [Accessed December 2004]

Aim

- To establish prescribing patterns and characteristics of use for non-selective NSAIDs (nsNSAIDs) and COX-2 selective inhibitors in Scottish general practice.

Continuous Morbidity Recording (CMR) Practices

- 55 CMR practices (with 362,155 registered patients) contributed data to Primary Care Clinical Informatics Unit - Research (PCCIU-R) on March 31st 2002
- GPs paid on a per capita basis since 1995 to collect all diagnoses and symptoms presenting to their practice.
- Practices record detailed information on prescribing.
- Accuracy and completeness maintained by the Information and Statistics Division[7].
- Practices are weighted to form a national sample broadly representative of the Scottish population as a whole in terms of age, sex, deprivation and urban/rural mix[7].

7. Anonymous. http://www.show.scot.nhs.uk/isdonline/CMR/Handbook/cmr_handbook.htm

Study Population

- Identified all registered patients who had ever been prescribed an NSAID, excluding aspirin.

Data Retrieved

- All relevant demographic, morbidity and prescribing data was retrieved for identified NSAID users over a 10-year period (1st April 1992 to 31st March 2002).

Prescribing data:

- All NSAID prescriptions
- Aspirin prescriptions

Morbidity data:

- Ischaemic Stroke (Read Code G68..)
- Coronary Heart Disease (Read Code G3…)

Analysis

- Population characteristics examined and described.
- Prescribing patterns for cox-2 inhibitors and conventional NSAIDs over a 10-year period (1st April 1992 to 31st March 2002) were determined.
- Characteristics of use for rofecoxib & celecoxib over a one-year period (1st April 2001 to 31st March 2002) were established.

Population

- Between 1st April 1992 to 31st March 2002:
  - 90,511 (25% registered patients) prescribed an NSAID at least once.
  - All NSAID users (100%) were prescribed non-selective NSAIDs.
  - 9,313 (10%) of NSAID users prescribed a cox-2 inhibitor.

Characteristics of NSAID users in Scotland

	Number of patients ever prescribed an NSAID (N=90,511)		Gender				Mean age (years)	
			Male		Female			
	n^p	%	n	%	n	%	Mean age	95% CI
nsNSAID population (1992/2002)	90,511	**100**	39384	**43.5**[a]	51127	**56.5**[a]	**50.1**	50.0 to 50.3
Cox-2 inhibitor population (1992/2002)	9,313	**10**	3231	**34.7**[a]	6082	**65.3**[a]	**59.0**	58.7 to 59.3
Rofecoxib user population (2001/2002)	3031	**8**[b]	1004	**33.1**[a]	2027	**66.9**[a]	**59.5**	58.9 to 60.0
Celecoxib user population (2001/2002)	1962	**5**[b]	677	**34.5**[a]	1285	**65.5**[a]	**59.5**	58.9 to 60.0

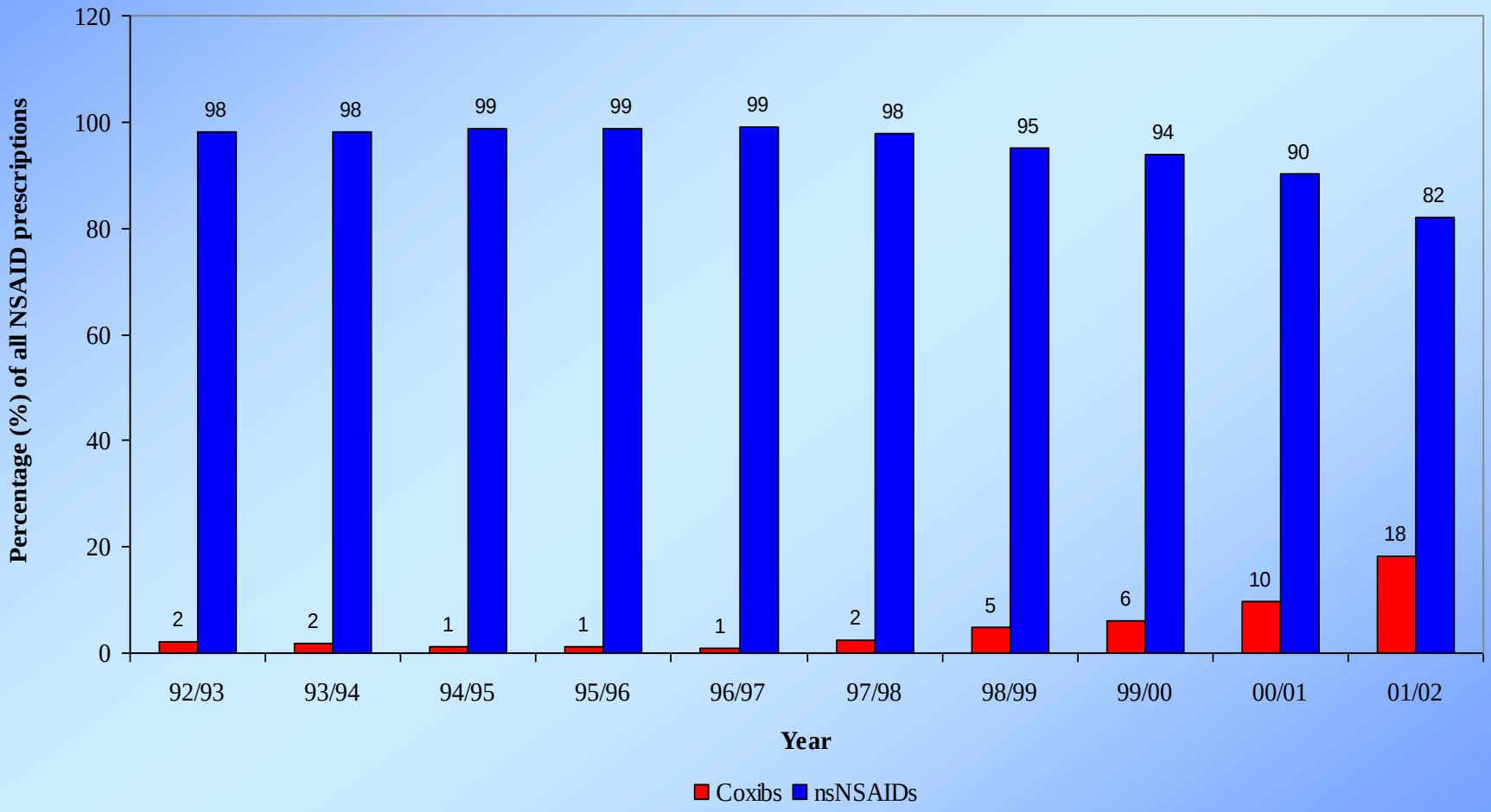
[a] N = n^p

[b] N = 39,615 (Number of patients ever prescribed an NSAID between 2001 to 2002.)

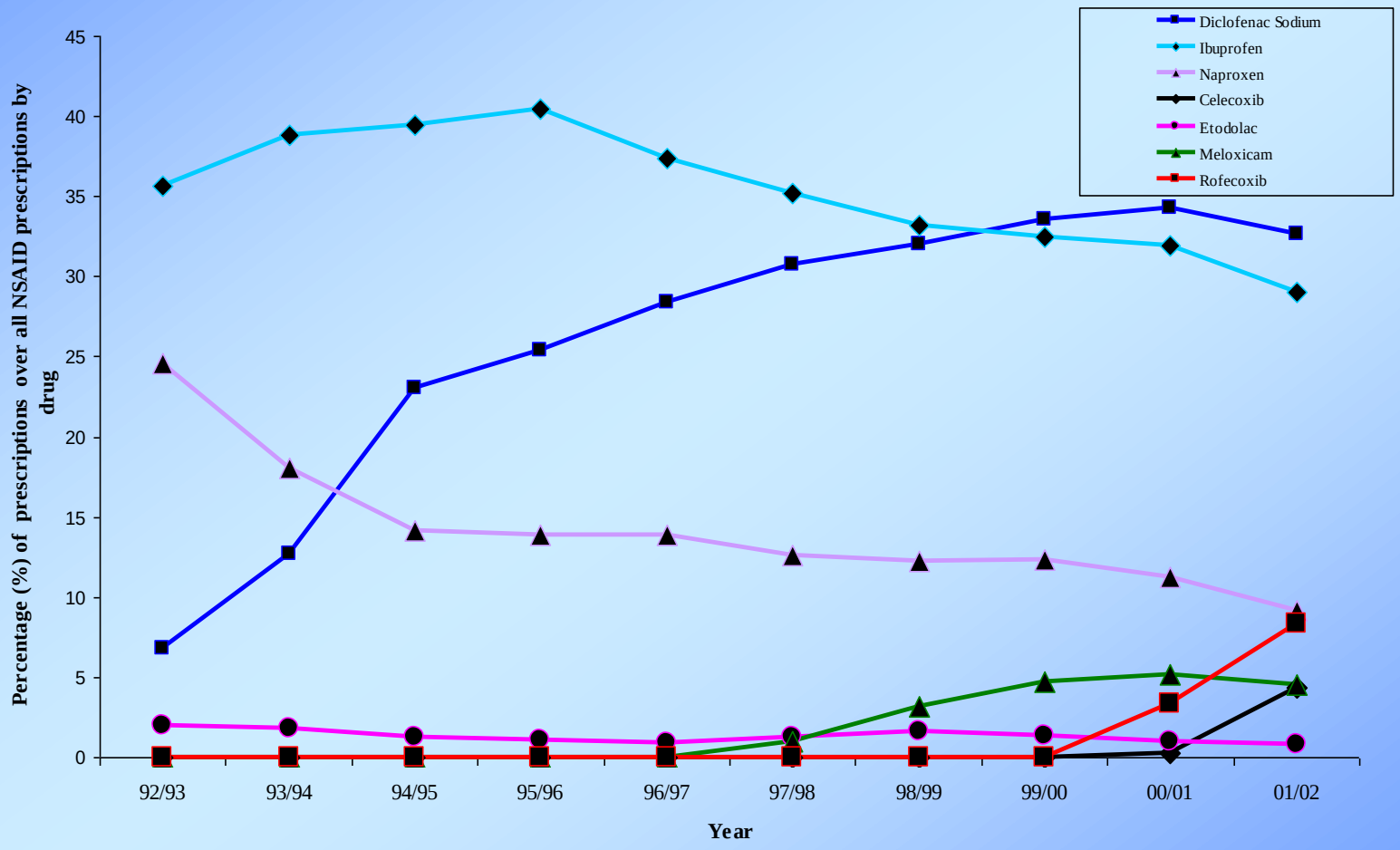
Selective and non-selective NSAID prescribing from introduction of new COX-2 selective inhibitors

- **April 1999 to March 2002:**
  - 6% of all prescriptions in Scottish general practice attributed to NSAIDs.
  - 88% of all NSAID prescriptions ⇒ conventional NSAIDs
  - 12% of all NSAID prescriptions ⇒ COX-2 inhibitors

Overall cox-2 inhibitor prescribing compared with non-selective NSAID prescribing, by year



Prescribing patterns of selective and non-selective NSAIDs between April 1992 to March 2002



Characteristics of rofecoxib and celecoxib use in Scotland (April 2001 to March 2002)

Of the rofecoxib users:

- 1.6% with history of ischaemic stroke
- 5.2% with history of CHD
- 18.7% prescribed aspirin

Of the celecoxib users:

- 1.1% with history of ischaemic stroke
- 6.2% with history of CHD
- 20.5% prescribed aspirin

Aspirin prescribed to:

- 63.8% of rofecoxib users with history of stroke
- 71.1% of rofecoxib users with a history of CHD

Aspirin prescribed to:

- 90.5% of celecoxib users with history of stroke
- 81.8% of celecoxib users with a history of CHD

Discussion

- Clinically significant proportion of patients prescribed coxibs have a history of cardiovascular disease,
  - Cardiovascular risk of coxibs
  - RA risk factor for cardiovascular disease
  - Potentially serious CV consequences for those not on aspirin.

- Large proportion of rofecoxib & celecoxib users with a history of CV disease are prescribed concomitant aspirin.
  - NICE Guidelines (2001)
  - Reduced gastroprotection

- Raises concerns regarding :-
  - prescribing practice
  - poor dissemination of findings to prescribers

8. Garret A & FitzGerald MD, (2004). Coxibs and cardiovascular disease. *N.Engl. J. Med*., **351** (17): 1709-1711.

NICE GUIDANCE COX-2 SELECTIVE INHIBITORS (July 2001)

- ‘Benefit of cox-2 inhibitors is reduced in patients taking concomitant low-dose aspirin and this combination is not justified.’

Conclusions

- Since their introduction, there has been a considerable uptake in the use of cox-2 selective inhibitors in Scottish general practice.
- A clinically significant number of patients with a history of stroke or CHD are being prescribed these agents.
- One fifth of patients prescribed cox-2 inhibitors are also prescribed aspirin.

Acknowledgements

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Pfizer Inc