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Cyclooxygenase-2 inhibitors and coronary occlusion – exploring dose–response relationships

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Aims
To investigate the relationship between acute coronary syndrome (ACS) and ingested doses of selective cyclooxygenase-2 (COX-2) inhibitors and other nonsteroidal anti-inflammatory drugs (NSAIDs).

Methods
Case–control study, commenced August 2003. Cases were patients admitted to hospital with ACS (myocardial infarction/unstable angina). Controls were hospital patients admitted for reasons other than acute vascular ischaemia or conditions that are believed to be complications of treatment with COX-2 inhibitors or NSAIDs. Structured interviews were undertaken within 7 days of admission, collecting information on cardiovascular events and risk factors and all ingested drugs, including the doses of COX-2 inhibitors and NSAID consumed in the previous week and month.

Results
An interim analysis of the data was conducted in late 2004 to inform a review of the COX-2 inhibitors by the Australian drug regulatory agency. Between August 2003 and October 2004, we recruited 328 ACS cases and 478 controls. With non-use of COX-2 inhibitors or NSAIDs as the reference the adjusted odds ratios (OR) for ACS were: celecoxib 1.11 (95% confidence interval 0.59, 2.11), rofecoxib 0.63 (0.31, 1.28) and other NSAIDs 0.67 (0.41, 1.09). Among control subjects, median daily ingested doses of celecoxib and rofecoxib were 200 mg and 13.4 mg, respectively. Using these to stratify risk, adjusted ORs for ACS were: 'low' dose (< median) 0.44 (0.19, 1.03); 'high' dose (≥ median) 1.22 (0.67, 2.21). A test for interaction across doses was statistically significant, OR 2.8 (1.0, 7.7), suggesting that at low doses, COX-2 inhibitors may be protective, becoming risk-inducing only at higher doses.

Conclusion
The possibility that the gradient of cardiovascular risk with COX-2 inhibitors runs from protective to risk-inducing has biological plausibility and merits further investigation.

Introduction

There has been intense interest in the relationship between use of relatively selective inhibitors of cyclooxygenase-2 (COX-2) and vascular ischaemic events [1, 2]. The increased risks seen in randomized placebo-controlled trials were associated mainly with high daily doses (25–50 mg of rofecoxib or 400–800 mg of celecoxib) [2–4]. Published pharmaco-epidemiological studies have documented the use of lower average doses in clinical practice [1, 5–10]. These studies have not documented consistently elevated relative risks of vascular occlusion, although estimates have been higher with rofecoxib than with celecoxib [1, 5–14].

The data are conflicting regarding the importance of dose in determining risk. In a meta-regression analysis of randomized trials of rofecoxib, Juni *et al.* found no effect of dose [2]. However, this review did not include recently published placebo-controlled trials that provided more definitive estimates of risk [3, 4]. Of the published controlled pharmaco-epidemiological studies of rofecoxib, several found higher estimated relative risks of vascular occlusion with daily doses >25 mg compared with ≤25 mg [1, 5, 9, 11, 13]. Only one study investigated the dose–response relationship with celecoxib and found no effect [9].

In Australia, celecoxib was listed on the government-subsidized Schedule of Pharmaceutical Benefits in August 2000. Rofecoxib was added in 2001. Uptake of these drugs was remarkable. By late 2001, overall usage was over 500 000 prescriptions per month, enough to treat over 10% of the population for 3 months in every year [15, 16]. While listing on the Schedule ensured wide availability, it also imposed restrictions on the quantities and doses of drugs that could be prescribed. The maximal monthly supplies that could be dispensed equated to a maximum daily dose of 200 mg of celecoxib (both 100-mg and 200-mg capsules were listed) and 25 mg of rofecoxib (both 12.5-mg and 25-mg tablets were listed). The prescribing restrictions led to many patients using doses below these maxima. This offered the opportunity to investigate vascular risks with relatively low doses of the drugs and to integrate these data with risk estimates from recent pharmaco-epidemiological studies [1, 5–13]. Given their capacity to inhibit COX-2, and with conflicting reports from observational studies on their association with vascular ischaemia [7, 17, 18], we included nonselective nonsteroidal anti-inflammatory drugs (NSAIDs) in the current study.

Methods

We undertook a case–control study to investigate the risk of acute coronary syndrome (ACS: acute myocardial infarction or unstable angina pectoris) with selective COX-2 inhibitors and conventional NSAIDs, paying particular attention to the doses of the drugs that were consumed in the period just before the coronary occlusive event. When the study commenced in August 2003, celecoxib and rofecoxib were the most widely used NSAIDs in Australia. Use of meloxicam was slight and valdecoxib, lumiracoxib and parecoxib were not marketed. The study was approved by the human research ethics committees of the Hunter Area Health Service and the University of Newcastle. The data presented here are from an interim analysis performed to assist the Australian drug regulatory authority (Therapeutic Goods Administration) in a review of the future registration status of selective COX-2 inhibitors following the withdrawal from the market of rofecoxib in September 2004. The study is ongoing and our intended final recruitment targets are 1200 cases with vascular ischaemia and 1800 controls which will give us a capacity to explore the relationships between ingested doses, degree of COX-2 selectivity and cardiovascular risk. The interim analysis included all 328 cases and 478 controls recruited up to September 2004. At this point, with a prevalence of exposure to COX-2 inhibitors of 11.5% amongst controls, the study had a power of around 80% to detect as significant ($P = 0.05$) an exposure odds ratio (OR) of <2.0.

Case patients were individuals admitted with ACS to three hospitals in the Hunter and Central Coast regions of New South Wales. These are the main hospitals serving a predominantly Caucasian population of just over one million persons. Cases had to meet the criteria for ACS developed by the PRISM study group (Box 1) [19]. They were identified through daily scrutiny of comput-

Box 1

PRISM criteria* for defining cases of acute coronary syndrome [19]

Myocardial infarction

An episode of chest pain, at least 20 min in duration, with new ST-T changes, new Q waves (>0.03 s in duration in two or more leads), or both, and an increase in the plasma troponin level

Unstable angina pectoris

Prolonged anginal pain or repetitive episodes of angina at rest, or during minimal exercise, in the previous 12 h and new transient or persistent ST-T ischaemic changes on the electrocardiogram [ST-segment elevation or depression of 0.1 mV or more, T-wave inversion of 0.3 mV or more in three or more limb leads or four or more precordial leads (excluding V1), or pseudonormalization of 0.1 mV or more] or an elevation of plasma troponin level

**Modified for use of plasma troponin rather than creatine kinase levels.*

erized admission lists, attendance at morning report and enquiries of the clinical staff working in medical and cardiology wards.

Controls were patients admitted acutely to the same hospitals, but who did not have acute vascular occlusion or gastrointestinal bleeding or ulcer perforation, diagnoses known to be associated with use of NSAIDs. Frequency matching was used to control for age and sex.

All cases and controls were interviewed by research nurses using a structured protocol and 'flash' cards with the generic and trade names of all selective COX-2 inhibitors, conventional NSAIDs, aspirin and paracetamol preparations available in Australia. While the nurses knew whether participants were cases or controls, they were trained to interview in a consistent, unbiased fashion. A series of open questions was used to determine if subjects used medicines for pain, followed, in the cases of users, by more direct questions to estimate the number of doses consumed in the week and month prior to the index day. Information was collected on medical history, smoking, alcohol intake and ingestion of all prescribed, over-the-counter and complementary medications. The interviews took between 20 and 30 minutes each to conduct and the same amount of time was needed to collect laboratory and clinical information from each medical chart. Fewer than 1% of potential case or control subjects approached declined to participate. During public holiday periods, recruitment was suspended. Where subjects were uncertain of taking a particular drug, we contacted their general practitioners (GPs) to confirm whether or not the drug was prescribed. All interviews were conducted within 7 days of the index date with over 90% performed within 4 days.

Univariate logistic regression was used to calculate the ratio of the odds of ACS with and without each of a series of demographic, disease and drug-exposure characteristics. Variables with ORs significantly different from 1 and clinical variables considered to be potential confounders were included in a multiple logistic regression model. A backward stepwise regression technique was used to generate a parsimonious model that retained age, gender and consumption of selective COX-2 inhibitors and conventional NSAIDs in the week before the index day. Variable exclusion was set at *P*-value of 0.1.

In the analyses of dose effects, we used the median doses consumed by controls to stratify all users as having taken 'low' or 'high' doses of the drugs. This minimized bias resulting from investigators selecting dose stratifications with prior knowledge of the data and ensured approximately equal numbers of controls in each of the comparison strata.

Results

Between August 2003 and October 2004, we recruited 328 cases of ACS and 478 controls. Despite frequency matching, cases were slightly older than controls and were more likely to be male (Table 1). As expected, cases had a higher prevalence of cardiovascular risk factors, use of low-dose aspirin and other antiplatelet and cardiovascular drugs than controls. The primary diagnoses of control subjects fell into the following categories: general surgical (29%), orthopaedic (27%), respiratory (23%) and other general medical (21%) problems.

Overall use of any anti-inflammatory drug (excluding low-dose aspirin) in the month prior to the index day was high: cases 26.8%, controls 28.9%. Use in the week preceding the index date was slightly lower: cases 22.0%, controls 26.4% (Table 1). After adjusting for age, gender, cardiovascular risk factors, aspirin and antiplatelet drug use, the odds ratios (*vs.* non-use) for ACS were not significantly elevated with ingestion of celecoxib, rofecoxib or conventional NSAIDs in the week prior to the index day (Table 1).

Average daily doses of selective COX-2 inhibitors consumed in the week before the index day by controls were relatively low: celecoxib 164.8 mg day^{-1}, rofecoxib 16.6 mg day^{-1}. Stratifying users according to the median doses consumed by controls in the previous week, 'low' dose users took <1400 mg $week^{-1}$ of celecoxib or <93.8 mg $week^{-1}$ of rofecoxib (equating to <200 mg day^{-1} or <13.4 mg day^{-1}, respectively), while 'high' dose users took the median dose or higher, ≥1400 mg $week^{-1}$ of celecoxib or ≥93.8 mg $week^{-1}$ of rofecoxib. For comparisons of 'high' with 'low' doses, the unadjusted ORs for ACS were 3.2 [95% confidence interval (CI) 0.9, 10.7] for celecoxib and 4.0 (0.9, 17.3) for rofecoxib. In the subsequent analyses of dose effects, we combined the drugs. The estimated OR for 'high' *vs.* 'low' doses of selective COX-2 inhibitors, after adjustment for age, sex, cardiac risk factors and coingestion of aspirin or other antiplatelet agents, was 2.8 (95% CI 1.0, 7.7).

With non-use of selective COX-2 inhibitors or conventional NSAIDs as the reference exposure category, the adjusted relative risk for 'low' doses of selective COX-2 inhibitors was 0.44 (0.19, 1.03) and for 'high' doses 1.22 (0.67, 2.21) (Table 2).

Discussion

We found no overall increase in the risk of ACS with ingestion of either rofecoxib or celecoxib, but there was an approximate threefold variation in the odds of ACS between individuals consuming 'high' and 'low' doses

Table 1
Unadjusted and multivariate estimates of acute coronary syndrome risk

Patient characteristics	Cases, $n = 328$ n (%)	Controls, $n = 478$ n (%)	Crude OR	95% CI (OR)	Adjusted OR	95% CI (OR)
Age (years)*	67.04 (56.55–76.75)	64.16 (52.81–75.13)	1.01	(1.00, 1.02)	1.01	(0.99, 1.02)
Male	209 (63.7)	282 (59.0)	1.22	(0.91, 1.63)	1.29	(0.93, 1.78)
Risk factors						
Hypertension	189 (58.6)	176 (36.8)	2.33	(1.75, 3.11)	1.84	(1.31, 2.56)
High cholesterol	169 (51.5)	107 (22.4)	3.68	(2.72, 5.00)	2.94	(2.11, 4.08)
Smoking						
Never	107 (32.6)	191 (40.0)				
Past	122 (37.2)	169 (35.4)				
Current	99 (30.2)	118 (24.7)	1.32	(0.96, 1.81)	2.08	(1.42, 3.05)
Of those who could recall dose						
NSAID use in the week before being in hospital						
None (reference)	256 (78.0)	352 (73.6)			1.00	
Celecoxib	23 (7.0)	27 (5.6)	1.17	(0.66, 2.09)	1.11	(0.59, 2.11)
Rofecoxib	15 (4.6)	28 (5.9)	0.74	(0.39, 1.41)	0.63	(0.31, 1.28)
Other NSAIDs	34 (10.4)	71 (14.9)	0.66	(0.42, 1.02)	0.67	(0.41, 1.09)
Aspirin	151 (46.9)	124 (2.9)	2.43	(1.81, 3.28)	1.77	(1.27, 2.47)
Antiplatelet drug	39 (11.9)	13 (2.7)	4.83	(2.53, 9.20)	3.42	(1.73, 6.79)

**Median (Q_1–Q_2). OR, Odds ratio; CI, confidence interval. Adjustment was made for age, gender, hypertension, elevated cholesterol, current smoking status, aspirin use and antiplatelet drug use in the logistic regression model.*

Table 2
Unadjusted and multivariate estimates of acute coronary syndrome risk with 'low' and 'high' doses of celecoxib and rofecoxib

Characteristics	Cases, $n = 328$ n (%)	Controls, $n = 478$ n (%)	Crude OR	95% CI (OR)	Adjusted OR	95% CI Patient (OR)
Of those who could recall dose						
NSAID use in the week before being in hospital						
None (reference)	256 (78.0)	352 (73.6)			1.00	
'Low' dose of celecoxib/rofecoxib*	8 (2.4)	26 (5.4)	0.42	(0.19, 0.95)	0.44	(0.19, 1.03)
'High' dose of celecoxib/rofecoxib*	30 (9.2)	29 (6.1)	1.42	(0.83, 2.43)	1.22	(0.67, 2.21)
Other NSAIDs	34 (10.4)	71 (14.9)	0.66	(0.42, 1.02)	0.67	(0.41, 1.08)

*Adjustment was made for age, gender, hypertension, elevated cholesterol, current smoking status, aspirin use and antiplatelet drug use in the logistic regression model. *'Low' dose users of celecoxib or rofecoxib ingested less than the median dose in the week before hospitalization; 'high' dose users ingested the median or higher. Median doses: celecoxib 1400 mg week^{-1}; rofecoxib 93.75 mg week^{-1}.*

of the drugs. While our study population had a high prevalence of use of selective COX-2 inhibitors, the median ingested doses were low, corresponding to <200 mg day^{-1} of celecoxib and substantially less than 25 mg day^{-1} of rofecoxib. The effects we observed are consistent with a gradient of risk ranging from a possible 'protective' effect at low doses to a 'risk-inducing' effect at higher doses. Because of small numbers, the results do not permit a precise quantification of risks at the extremes of dose, but they are consistent with a true biological effect and suggest that the relationships may be more complex than previously thought.

Table 3
Observational studies: adjusted relative risk estimates (95% confidence interval) for cardiovascular ischaemia with selective cyclooxygenase-2 inhibitors

Citation	Exposure	All celecoxib	All rofecoxib	Rofecoxib ≤ 25 day^{-1}	Rofecoxib > 25 day^{-1}
Singh *et al.* [5]	Jan. 1999 to June 2004	1.09 (1.02, 1.15)	1.32 (1.22, 1.42)	1.16 (no CI)	2.4 (no CI)
Sturkenboom *et al.* [6]	1999–2004	NR	1.52 (1.08, 2.15)	NR	2.32 (1.2, 4.4)‡
Hippsley-Cox & Coupland [7]	Aug. 2000 to July 2004	1.21 (0.96, 1.54)	1.32 (1.09, 1.61)	NR	NR
Johnsen *et al.* [8]	Jan. 2000 to Dec. 2003	1.25 (0.97, 1.62)	1.80 (1.47, 2.21)	NR	NR
Levesque *et al.* [9]	Jan. 1999 to June 2002	0.99 (0.85, 1.16)	1.24 (1.05, 1.46)	1.21 (1.02, 1.43)	1.73 (1.09, 2.76)
Kimmel *et al.*[10]	May 1998 to Dec. 2002	0.43 (0.23, 0.79)	1.16 (0.70, 1.93)	NR	NR
Graham *et al.* [1]	Jan. 1999 to Dec. 2001	0.84 (0.67, 1.04)	1.34 (0.98, 1.82)	1.23 (0.89, 1.71)	3.00 (1.09, 8.31)
Solomon *et al.* [11]	Jan. 1999 to Dec. 2000	0.93 (0.84, 1.02)	1.14 (1.00, 1.31)	1.21 (1.01, 1.44)*	1.70 (1.07, 2.71)†
Mamdani *et al.* [12]	Apr. 1998 to Mar. 2001	0.90 (0.70, 1.2)	1.0 (0.8, 1.4)	NR	NR
Ray *et al.* [13]	Jan. 1999 to June 2001	0.96 (0.76, 1.21)	NR	1.03 (0.78, 1.35)	1.70 (0.98, 2.95)
Pooled risk estimate	Random effects	0.99 (0.90, 1.09)	1.30 (1.18, 1.44)	1.18 (1.06, 1.32)	1.85 (1.44, 2.36)
	Fixed effects	1.03 (0.98, 1.08)	1.30 (1.23, 1.37)	1.18 (1.06, 1.32)	1.85 (1.44, 2.38)

The reference exposure category in these calculations was no (or remote) use of any anti-inflammatory drug. The analysis excludes the study of Shaya et al. *[14] owing to use of nonselective nonsteroidal anti-inflammatory drugs as the reference exposure category.*
*CI, 95% confidence interval; NR, not reported. *Celecoxib ≤200 mg day^{-1}was the reference exposure category. †Celecoxib >200 mg day^{-1}was the reference exposure category. ‡Twice the 'recommended daily dose'. Only Levesque* et al. *[9] provided data on celecoxib doses: ≤200 mg day^{-1}adjusted rate ratio 0.98 (0.83, 1.17); >200 mg day^{-1}1.00 (0.78, 1.29). Sturkenboom* et al. *[6] reported rofecoxib was associated with an increased risk of stroke/transient ischaemic attack but not myocardial infarction/sudden cardiac death; only the risk estimate for the former was reported and these are the values in the table.*

At least 10 controlled pharmaco-epidemiological studies of the risks of vascular occlusion with COX-2 inhibitors have been published since 2002 [1, 5–14]. Excluding those published in abstract form [5, 6] (which provided insufficient detail), the remaining eight studies recruited 46 877 individuals with cardiovascular events, of whom 2249 (4.8%) had used a COX-2 inhibitor in the previous week or month. The results of these studies are summarized in Table 3 [1, 5–13]. The pooled relative risk estimate for celecoxib suggests that there is no increase in risk at the typical doses used by the study populations. Only one study [9] reported the effects of varying doses of celecoxib and found no difference in myocardial infarction risk between daily doses of ≤200 mg and >200 mg. In contrast, rofecoxib was associated, on average, with a 30% increase in risk of vascular occlusion, with a clear-cut dose–response. The estimates for celecoxib and rofecoxib have non-overlapping CIs indicating that the difference is statistically significant (Table 3).

It is not possible to make a direct comparison between these results and the data from our study. We were unable to estimate relative risks with doses above 200 mg celecoxib and 25 mg rofecoxib, as almost none of our participants consumed these amounts. Consequently, we had to stratify our analyses of dose at lower values. These analyses, which were not performed in other studies, raised the possibility of a protective effect of COX-2 inhibitors at low doses. The published studies summarized in Table 3 neither support nor refute this suggestion, as they have not reported comparable dose analyses. However, Kimmel *et al.* found an apparent protective effect of celecoxib [10].

A number of limitations apply to our study and the results should be viewed with appropriate caution. These are preliminary analyses from an ongoing study. Consequently, statistical power is limited and the findings may not be replicated in the final dataset. However, the magnitude of the variation in risk between 'high' and 'low' doses suggests that a real difference exists. Our dosage information was based on face-to-face interviews. Recall bias is possible but we sought to minimize this by asking about all medications taken and by interviewing cases and controls in a standardized fashion. All the interviews were conducted close to the index day. Where there was uncertainty about use of a medication,

we checked with the patient's GP. Direct interview also permitted us to account for self-medication with aspirin and NSAIDs. Our estimates of use are likely to be more accurate than those inferred from electronic dispensing records, where it has to be assumed that medicines dispensed are ingested and that dosing instructions are adhered to. Electronic dispensing records linked to hospital discharge diagnosis coding records were used by all but one of the published pharmaco-epidemiological studies [1, 5–9, 11–14]. Kimmel *et al.* interviewed subjects by telephone up to 4 months following the index event [10].

Accepting that our data are not conclusive, a protective effect of low doses of celecoxib or rofecoxib is plausible based on what is known about the complex biology of cyclooxygenase in different tissue compartments including the vascular endothelium, myocardium and atherosclerotic plaques. The rationale for the development of COX-2 selective anti-inflammatory drugs was the inhibition of the inflammatory COX-2 product, prostaglandin E_2 (PGE_2) in one compartment (an inflammatory site) with sparing in a separate compartment (the stomach). This focus on PGE_2 has detracted from the observation that cyclooxygenase, whether COX-1 or COX-2, can produce multiple eicosanoids. This occurs because the immediate product of COX activity on arachidonic acid is PGH_2. From PGH_2, terminal synthases produce eicosanoids including thromboxane, PGE_2 and prostacyclin (PGI_2). In studies of human vascular endothelial cells, the activity of terminal synthases has been found to vary with concentration of the PGH_2 substrate [20]. When total cyclooxygenase activity is low and PGH_2 levels are consequently low, thromboxane is produced preferentially over prostacyclin. When PGH_2 levels are high, irrespective of whether this is due to COX-1 or COX-2 activity, prostaglandin synthases respond with increased production of prostacyclin (and PGE_2), but thromboxane synthase becomes saturated [20, 21]. Depending on the levels of the common PGH_2 precursor, it is possible that in the endothelial cell compartment low levels of cyclooxygenase inhibition could preferentially decrease thromboxane synthesis but preserve prostacyclin synthesis, tipping the balance in favour of vascular protection. Higher levels of inhibition, however, would block prostacyclin synthesis, with ischaemic consequences in vulnerable individuals.

A protective to risk-inducing gradient of cardiovascular effect has been described with aspirin, albeit in an animal model of myocardial ischaemia. COX-2 appears to pay an obligatory role in ischaemic preconditioning, an innate response to stress wherein brief episodes of sublethal ischaemia render the heart relatively resistant to subsequent ischaemic stresses [22, 23]. While COX-2 is normally expressed at low levels in the myocardium, it is upregulated in ischaemic preconditioning and mediates the protective effects of the late phase of ischaemic preconditioning against both myocardial stunning and infarction. These benefits appear to be the result of increased levels of prostacyclin and PGE_2 [22]. Irreversible blockade of platelet cyclooxygenase is the mechanism by which low-dose aspirin is cardioprotective. In the animal model, both antithrombotic and analgesic doses of aspirin inhibited platelet aggregation and did not interfere with the late phase of ischaemic preconditioning, although they exerted a partial block on COX-2 activity [23]. High (antirheumatic) doses of aspirin, sufficient to block completely the increased COX-2 activity, led to loss of the protective effects of late-phase ischaemic preconditioning. The observation led the authors to caution on the use of high doses of aspirin in patients with atherosclerotic disease on the basis that they might deprive the heart of its innate defensive response. No human studies have investigated the effects of low- *vs.* high-dose aspirin (and hence low *vs.* high levels of COX-2 blockade) on cardiovascular outcomes, nor, for that matter, the effects of low *vs.* high doses of selective COX-2 inhibitors or conventional NSAIDs.

Illustrating the complexity of cyclooxygenase function and the importance of understanding its activities in different compartments is the observation that in atherosclerotic plaques, as in other sites of inflammation, expression is upregulated. Macrophages produce plaque-destabilizing metalloproteinases in response to upregulated COX-2 expression and consequent prostaglandin production [24]. Selective COX-2 inhibitors have been variously reported to inhibit [25], accelerate [26] or have no effect [27, 28] on atherogenesis in animal models. Dose effects were not explored in these studies. Adding to the complexity, the combination of a COX-2 inhibitor and a thromboxane receptor antagonist altered plaque morphology, possibly predisposing to destabilization [28].

The picture may be further complicated by genetics. Polymorphisms of the COX-2 gene associated with reduced COX-2 expression, and hence reduced metalloproteinase production in atherosclerotic plaques, have been associated with a reduction in the risk of myocardial infarction and strokes [29, 30]. Theoretically, individuals with the more active alleles may benefit from a 'plaque-stabilizing' effect of COX-2 inhibition.

The idea that low levels of cyclooxygenase inhibition might be cardioprotective is supported by the discovery that olive oil, long credited with making a major contri-

bution to the health benefits associated with a Mediterranean diet, has cyclooxygenase-blocking effects [31]. The responsible component is oleocanthal, the daily dose of which in the average Mediterranean diet would correspond to low doses of ibuprofen (estimated at about 10% of the analgesic dose). Oleocanthal blocks both COX-1 and COX-2 in a dose-dependent fashion.

The physiological and pathological roles of COX-2 are clearly complex and remain to be fully elucidated. The emerging evidence suggests that COX-2 functions and the impacts of inhibition vary depending on the level of induction, degree of inhibition, relative amounts of eicosanoids produced, site of production and COX-2 genotype. Our data, along with those emerging from the animal studies, suggest that investigation of the cardiovascular impacts of selective COX-2 inhibition needs to include evaluation of the effects of differing degrees of inhibition.

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