KRITISCHES LESEN WISSENSCHAFTLICHER LITERATUR – ERGEBNISSE FINDEN, BEURTEILEN UND IN DIE PRAXIS INTEGRIEREN

Materialien und Aufgaben

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PARACETAMOL ALS WOLF IM SCHAFSPELZ – EIN FALLBEISPIEL

Hintergrund

Paracetamol, Ibuprofen und Acetylsalicylsäure sind die am häufigsten verwendeten Arzneimittel in Deutschland. Zahlreiche Studien und insbesondere die Erkenntnisse zum kardiovaskulären Risikoprofil von selektiven und nichtselektiven Cox-Hemmern haben auch die nicht verschreibungspflichtigen Analgetika wieder in die Diskussion gebracht.

Paracetamol zur oralen Anwendung wurde im April 2009 in Packungen mit mehr als 10g der Verschreibungspflicht unterstellt. Im Januar 2010 hatte der Sachverständigenausschuss für Verschreibungspflicht empfohlen, alle zurzeit noch apothekenpflichtigen Analgetika ab einer bestimmten Packungsgröße der Verschreibungspflicht zu unterstellen, was bisher nicht umgesetzt wurde.

Man weiß, dass die unkritische Anwendung von Paracetamol größere Risiken beinhaltet als bisher angenommen. Höhere Dosen können bereits über kürzere Zeit zu Leberschädigung führen. In Studien wurde gezeigt, dass die Langzeiteinnahme von Paracetamol zu erhöhtem Blutdruck und einer höheren Rate an kardiovaskulären Ereignissen führen kann, vergleichbar zu anderen NSAR und den Cox II-Hemmern.

Das Problem?

Paracetamol ist nicht so harmlos wie es scheint. Die Frage ist, ob es zu einer neuen Nutzen-Risiko-Bewertung der Substanz kommen sollte. Eine Stellungnahme des Bundesverbandes der Arzneimittelhersteller (BAH) sieht jedoch keinen Anlass zur grundsätzlichen Neubewertung oder der Änderung der Verschreibungspflicht (Bundesverband Deutscher Arzneimittelhersteller 2010).

AUFGABE 1: DAS FELD ABSTECKEN

Sie finden auf den folgenden Seiten einen Artikel von Prof. Dr. Kay Brune (Brune 2010). Welche „sieben Wölfe im Schafspelz“ hat der Pharmakologe identifiziert? Welche davon halten Sie für besonders relevant? Warum?

AUFGABE 2: DIE KLINISCHE FRAGE DEFINIEREN

Nachdem Sie geklärt haben, worum es eigentlich geht und was Sie wissen wollen, definieren Sie eine klinische Frage, die durch die Literatur beantwortbar ist.

1. Um welche Patienten/Personen geht es?

2. Um welche Intervention geht es? Mit welcher Intervention soll verglichen werden?

3. Definieren Sie das unerwünschte Ereignis.

AUFGABE 3: DIE STUDIE BEWERTEN. DIE ORIGINALITÄT DER STUDIE BEURTEILEN

Wir nehmen uns jetzt die Studie Sudano (Sudano et al.) besonders genau vor. Nutzen Sie die untenstehende Tabelle aus White (White et al.), um die folgenden Fragen zu beurteilen

Kann ich durch die Studie etwas erfahren, was ich vorher nicht wusste?

Sind die Methoden besser als bisher?

- Ist die Studie größer, ist das Follow-up länger, vollständiger? Werden methodische Probleme bisheriger Studien gelöst?
- Sind das andere Teilnehmer als bisher?
- Ist die Fragestellung hinreichend relevant? Braucht man die Studienergebnisse, um bestehende Praxis neu zu bewerten?

Table. Effects of Various NSAIDs on Ambulatory BP

Study	Design and Trial Duration	Patient Population	n	Age, y	Study Drugs	Baseline 24-H BP, mm Hg	Change in 24-h BP, mm Hg
Izhar et al[7]	Randomized, crossover, active controlled, 8 wk	Hypertensive	25	58	Celecoxib 200 mg QD	129/80	1.6/1.9
		Osteoarthritis		58	Diclofenac 75 mg BID	129/79	4.2*/3.0*
MacDonald et al[24]	Parallel, double-blind, active controlled, 4 wk	Osteoarthritis	787	65	Lumiracoxib 100 mg QD	127/74	−2.7/−1.5
		Hypertensive		64	Ibuprofen 600 mg TID	127/74	2.2*/0.5*
Morgan et al[25]	Parallel, randomized, double-blind, crossover, 6 wk	Hypertensives Nonarthritis	41	69	Amlodipine+indomethacin 50 mg BID	141/77	1.0/0.0
				72	Enalapril+indomethacin 50 mg BID	134/73	12.0*/5.0*
Polonia et al[26]	Randomized, crossover, single-blind, 1 wk of NSAID	Hypertensives	18	53	Nifedipine+indomethacin 75 mg	135/88	0.3/0.6
		Nonarthritis		53	Enalapril+indomethacin 75 mg	135/87	6.8*/4.6*
Schwartz et al[27]	Parallel, double-blind, placebo-, and active-controlled, 15 d	Elderly normal	85	66	Etoricoxib 90 mg QD	NR	7.7*/3.2*
		Controlled diet		65	Celecoxib 200 mg BID	NR	2.4*/1.1
				67	Naproxen 500 mg BID	NR	3.6*/1.4*
				66	Placebo	NR	−2.4/−0.8
Sowers et al[8]	Parallel, double-blind, active-controlled, 6 and 12 wk	Osteoarthritis	404	64	Rofecoxib 25 mg QD	132/76	4.2*/1.5*
		Hypertension		62	Celecoxib 200 mg QD	132/76	−0.1/−0.1
	Type 2 diabetes mellitus			64	Naproxen 500 mg BID	134/76	−0.8/−1.0
Sudano et al[15]	Randomized, double-blind crossover, placebo-controlled, 2 wk	Coronary artery disease	33	61	Acetaminophen 1 g TID	122/73	2.9*/2.2*
				61	Placebo	123/74	−0.5/0.2
White et al[6]	Parallel, double-blind, placebo-controlled, 4 wk	Hypertensive	178	55	Celecoxib 200 mg BID	135/84	2.6/1.5
		On ACE inhibitor		53	Placebo	131/82	1.0/0.3

DM indicates diabetes mellitus; ACE, angiotensin-converting enzyme.
*Statistically greater than comparator.

AUFGABE 4: DIE STUDIE BEWERTEN. EINSCHLUSS- UND AUSSCHLUSSKRITERIEN

Wer wurde in die Studie eingeschlossen? Wer wurde ausgeschlossen? Woher wurden die Teilnehmer rekrutiert? War das ein „real life“ Szenario?

Study Population

The patients were recruited at the Cardiovascular Center Cardiology, University Hospital Zurich, Zurich, Switzerland. Patients with CAD (documented by coronary angiography, nuclear imaging, or positive stress test) on stable cardiovascular medication for at least 1 month who were between 18 to 80 years of age and gave written informed consent were included in the study.

Exclusion criteria were acute myocardial infarction, unstable angina, stroke, or coronary intervention/revascularization procedure within 3 months before study entry; left ventricular ejection fraction <50%; use of other analgesics (platelet inhibition therapy with aspirin 100 mg/d was continued); chronic pain; smoking, alcohol, or substance abuse; uncontrolled BP despite adequate therapy (>160/100 mm Hg); renal failure (serum creatinine >200 μmol/L); liver disease (alanine aminotransferase or aspartate aminotransferase >100 IU); acute hepatitis; hyperbilirubinemia; concomitant therapy with oral anticoagulants, Phenobarbital, phenytoin, carbamazepine, isonicotinic acid, chloramphenicol, chlorzoxazone, zidovudine, and salicylamide; long-term use of nitrates; insulin-dependent diabetes mellitus; anemia (hemoglobin <10 g/dL); known allergies to acetaminophen; systemic inflammatory diseases (eg, rheumatoid arthritis, Crohn's Disease); and participation in another study within the last month. The patients were not allowed to take any drugs other than the background cardiovascular therapy (in particular, no anti-inflammatory and pain-relieving drugs) to secure the double-blind design.

Aus (Sudano et al.)

AUFGABE 5: DIE STUDIE BEWERTEN. STUDIENDESIGN

Stellen Sie fest, welche Intervention untersucht wurde und womit man sie verglichen hat. Welche(s) Outcome(s) wurde(n) untersucht und wie gemessen?

After screening and recruiting, the patients were randomly assigned to 2 groups. For randomization, an unpredictable allocation sequence was provided by external institutions (InterCorNet and Cantonal Pharmacy, both in Zurich, Switzerland), which were responsible for the blinding and labeling of the drugs. All investigators were unaware of the allocation procedure at any time. The patients were randomized to receive either acetaminophen 1 g TID, a typical dose for pain relief, or matching placebo for 2 weeks in the first part of the study or vice versa in the second part. Between the first and the second parts was a washout period of 2 weeks.

At each visit (baseline and after 2, 4, and 6 weeks), ABP and endothelial function were measured, blood samples were drawn, 24-hour urine was collected, clinical status was assessed, and adverse events were recorded. At each visit, a safety analysis was performed, including the assessment of electrolytes and of liver and kidney function, plus a white and red blood cell count. Pregnancy testing in women with child-bearing potential was performed only at the first visit. The patients were advised not to take their usual drugs in the morning of the examination day (all examinations and measurements were performed in the morning). Blood samples were taken and flow-mediated dilatation (FMD) was assessed before the patients took their medications. The regular medications and study drug were taken thereafter and before the 24-hour ABPM was placed.

The study drug and placebo were prepared in identical capsules to ensure uniform appearance of both formulations. The verum consisted of pure acetaminophen and did not contain sodium, with the exception of a 3% solution containing sodium lactate on the capsule surface. According to the manufacturer, this amount of sodium is not measurable in vivo. The placebo preparation contained D-mannitol only. The Ethics Committee of the Canton Zurich and the Swiss Agency for Therapeutic Products (Swissmedic) approved the study protocol. The study was registered at http://www.clinicaltrials.gov (identifier: NCT00534651).

ABP Measurement

ABP measurements were obtained over 24 hours with the Tracker NIBP 2 (Delmar, Del Mar Reynolds Medical, Hertford, UK) before and after the active treatment phase according to recent guidelines.[9] Patients were asked to keep their arm calm while the cuff was inflating and to avoid excessive physical exertion during monitoring. The monitors were programmed to take readings every 15 minutes during daytime and every 30 minutes during nighttime.

AUFGABE 6. DIE STUDIE BEWERTEN. STATISTIK

Wurde eine Fallzahl- oder Powerberechnung durchgeführt?

The primary end points were the changes in mean 24-hour systolic ABP (SBP) and diastolic ABP (DBP) and the change in FMD after 2 weeks of treatment with acetaminophen compared with placebo. After evaluation of the first 22 patients, the analysis demonstrated insufficient power for the results on BP measurements. Therefore, using the data obtained so far (SD of the difference, 4.9 mm Hg;

minimal detectable difference in means, 2.5 mm Hg), we calculated the sample size needed (33 patients) for an 81% statistical power and a significance level of 0.05 (2 sided) for this crossover study.

War das Follow-up lange genug?

Because patients included in the study did not present with pain and thus would potentially not benefit from the study drug, the number of patients investigated had to be limited to the minimal number determined by a preliminary power calculation. In addition, to limit the number of patients to exposure to a drug from which they potentially would not benefit, a "crossover" design was chosen.

War das Follow-up vollständig?

AUFGABE 7. DIE STELLUNGNAHME DES BAH EINORDNEN

Hier finden Sie den Ausschnitt aus der Stellungnahme des BAH, der sich mit dem kardiovaskulären Risikopotenzial von Paracetamol auseinandersetzt. Versuchen Sie, mit Hilfe der angefügten Ausschnitte folgende Fragen zu beurteilen:

1. Untersucht Forman et al. (Forman et al. 2005) Herzinfarkte und Schlaganfall?

2. Ist White und Campbell (White and Campbell) ein Editorial zu Forman et al (Forman et al. 2005)?

3. Ist der Dosisbereich, der von Chan et al. (Chan et al. 2006) untersucht wurde, unrealistisch? Warum oder warum nicht?

Brune führt insgesamt 19 Literaturstudien an, die seiner Meinung nach eine Neubewertung des Nutzens und der Risiken von Paracetamol erforderlich machen. Im Rahmen dieser Stellungnahme können selbstverständlich nicht alle Artikel und die darin diskutierten Studien erläutert werden. Viele der zitierten Studien weisen methodische Schwächen oder andere Mängel auf; einige der zitierten Arbeiten enthalten überhaupt keine Daten zu Paracetamol, sondern fassen andere – ebenfalls zitierte – Arbeiten nur erneut zusammen. So stellt die Arbeit von White und Campbell [Zitat 7] lediglich ein Editorial zu Forman et al. [Zitat 6] dar. Die im Zusammenhang mit dem dritten Vorwurf – vermehrtes Auftreten von Herzinfarkten und Schlaganfällen unter Paracetamol – zitierte Arbeit von Forman et al. [Zitat 6] untersuchte erst gar nicht die Assoziation einer Paracetamol-Einnahme mit Herzinfarkten und Schlaganfällen; die daraus abgeleiteten Empfehlungen können daher auch nicht einen solchen Zusammenhang belegen. Die Arbeit von Chan et al. [Zitat 8], die eine Kohorte US-amerikanischer Krankenschwestern über zwölf Jahre lang befragt hat, fand eine Assoziation einer NSAIDs-Einnahme und dem erhöhen Risiko kardiovaskulärer Ereignisse erst dann, wenn das Arzneimittel an mehr als an 22 Tagen pro Monat eingenommen wurde. Eine solche Dauereinnahme fällt zweifelsohne nicht in den Anwendungsbereich rezeptfreier Analgetika und kann daher auch nicht herangezogen werden, um zu begründen, dass verschreibungsfreie Produkte der Rezeptpflicht unterstellt werden sollen.

Aus (Forman et al. 2005)

Acetaminophen, ibuprofen, and aspirin are the 3 most frequently used drugs in the United States.[1] These drugs may lead to high blood pressure through various mechanisms, including inhibition of vasodilatory prostaglandins.[2–5] In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) increase renal sodium reabsorption,[6–8] and acetaminophen and NSAIDs may impair endothelial function.[9–17]

In 2 large prospective cohorts of women, we previously reported an association between the frequency of analgesic use (days per month) and the risk of developing hypertension.[18,19] The major criticisms of these previous analyses were the lack of information on drug doses used by participants and the indications for their use, in particular, the concern that headache as a result of higher blood pressure may lead to analgesic use (confounding by indication).

To address these concerns and to further examine this important public health issue, we studied the association between dose of nonnarcotic analgesic drug use, indication for use, and the risk of incident hypertension among subcohorts consisting of 1903 older female participants of Nurses' Health Study I (NHS I) and 3220 younger female participants of NHS II without a history of hypertension at baseline.

In this issue of *Circulation*, the findings of Sudano and coworkers[15] cast some doubt on the cardiovascular safety of acetaminophen, at least from the perspective of BP. The investigators evaluated the effects of acetaminophen at a standard osteoarthritis dose (1 g TID) on ambulatory BP, a variety of serum biomarkers, and platelet and vascular function in 33 patients with known coronary artery disease using a randomized, double-blind, placebo-controlled crossover design. Even with truncated treatment phases of 2 weeks (The investigators wished to minimize exposure time to acetaminophen because these subjects had no pain indication), acetaminophen induced statistically significant increases in mean 24-hour systolic and diastolic BPs from baseline compared with placebo (≈3/2 mm Hg). This increase in 24-hour mean BP is not dissimilar to changes observed with many of the NSAIDs (the Table). Additionally, a small but significant increase in 24-hour heart rate (2 bpm) occurred on acetaminophen relative to placebo.

Aus (White and Campbell)

Assessment of Medication Use

As previously described,[37] beginning in 1990 we asked women if they regularly used aspirin, other antiinflammatory drugs "(eg, ibuprofen, Naprosyn [Roche Pharmaceuticals, Nutley, NJ], Advil [Wyeth, Madison, NJ])," and acetaminophen "(eg, Tylenol [McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, Pa])," and the frequency of use. We updated these data biennially; beginning in 1998, for each agent, we also asked participants the number of tablets used per week. Early in the study, most women used standard-dose aspirin tablets; however, to reflect overall trends in consumption of low-dose aspirin, questionnaires after 1992 asked participants to convert intake of 4 "baby" aspirin to 1 adult tablet, and in 2000 we inquired specifically about baby or low-dose aspirin. COX-2 inhibitors were not introduced in the United States until 1999; hence, we first asked women in 2000 to report if they regularly used "Celebrex (Pfizer Inc, New York, NY) or Vioxx (Merck & Co Inc, West Trenton, NJ) (COX-2 inhibitors)" but did not inquire specifically about frequency or dose.

In a subsample of 200 women who reported aspirin use in 1990, we conducted a study to determine the reasons for use (91% response). The major reasons for use among women taking 1 to 6 and ≥7 aspirin tablets per week were headache (32% and 18%, respectively); arthritis and other musculoskeletal pain (30% and 50%); a combination of headache and musculoskeletal pain (16% and 15%); cardiovascular disease prevention (9% and 8%); and other reasons (13% and 9%).[38]

In 1999, we also sent a supplementary questionnaire to 4238 of the participants (91% response) to ascertain a 10-year detailed history of analgesic use.[39] Among aspirin users, 67% typically used 1 tablet per day, and 75% typically used tablets >300 mg. Among NSAID users, 73% used ibuprofen, 14% used naproxen, and 13% used other type; 53% typically used 2 tablets per day, 25% used 1 tablet per day, and 22% used ≥3 tablets per day. Among ibuprofen users, 62% reported using tablets between 100 and 299 mg. Among acetaminophen users, 55% typically used 2 tablets per day, 18% used 1 tablet per day, and 26% used ≥3 tablets per day; 69% used tablets of ≥500 mg. The major reasons for use among ibuprofen and acetaminophen users were muscle/joint pain (84% and 65%, respectively); headache (5% and 24%); backache (5% and 4%); and other reasons (6% and 8%).

Aus (Chan et al. 2006)

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Sie sind hier: DAZ.online Umfrage

Aktuelle Umfrage zu Paracetamol

In einem Gastkommentar in DAZ 2010, Nr. 49, S. 42-43, mit dem provozierenden Titel „Paracetamol: Ein Wolf im Schafspelz läuft frei herum!“ hat der Erlanger Pharmakologe Prof. Dr. Dr. Kay Brune festgestellt, dass es an der Zeit sei, Paracetamol vom Markt zu nehmen oder ihm wenigsten das Prädikat rezeptfrei zu entziehen. Begründet hat er dies unter anderem mit neuen Studien, die auf ein erhöhtes kardiovaskuläres Risiko und besondere Risiken bei Anwendung in der Schwangerschaft hindeuten. Der Bundesverband der Arzneimittelhersteller (BAH), teilt diese Auffassung nicht und erklärt in einer Stellungnahme in DAZ 2010, Nr. 50, S. 69, warum diese von Brune angeführten Studien seiner Meinung nach keine neue Risikoeinstufung rechtfertigen.

Paracetamol – ein Wolf im Schafspelz?

Frage: Wie ist Ihre Meinung?

- Die Risiken von Paracetamol werden überbewertet, eine Rezeptpflicht ist in keiner Weise gerechtfertigt. Die Begrenzung der Packungsgröße muss rückgängig gemacht werden.
- Die erfolgte Unterstellung von Packungen mit mehr als 10 g Paracetamol unter die Verschreibungspflicht reicht aus, um eventuellen Missbrauch zu verhindern und potenzielle Risiken zu minimieren.
- Um Missbrauch zu verhindern und Risiken zu minimieren, muss Paracetamol vollständig der Verschreibungspflicht unterstellt werden.
- Paracetamol ist eine obsolete Substanz. Sie muss vom Markt genommen werden.

Ihr Kommentar zu dieser Umfrage:

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DAZ 49 / 09.12.2010

GASTKOMMENTAR

Paracetamol: Ein Wolf im Schafspelz läuft frei herum!

Neue Studien zur Paracetamol-Einnahme in der Schwangerschaft haben Prof. Dr. Dr. Kay Brune vom Institut für Experimentelle und Klinische Pharmakologie und Toxikologie, der Universität Erlangen-Nürnberg veranlasst, sich die Studienlage zu Paracetamol noch einmal genauer anzuschauen. Im folgenden Gastkommentar untermauert er seine Forderung, Paracetamol zumindest vollständig der Rezeptpflicht zu unterstellen.

Prof. Dr. Dr. Kay Brune

Die Meisten von uns sind mit Märchen aufgewachsen und daher mit dem bösen Wolf (auch im Schafspelz) bestens vertraut. Er tritt scheu und milde wie ein Lämmchen auf, ist jedoch äußerst gefährlich. Wir kennen den bösen Wolf auch aus der Geschichte von den sieben Geißlein, die ihn in dem Glauben, er sei ungefährlich, in das Haus ließen, um dann von ihm gefressen zu werden. Immerhin genügte ein Schnitt in den Bauch dieses Wolfes, um die hübschen, kleinen, weißen Zicklein wieder zu Tage zu fördern.

Jahrzehntelang glaubten wir (auch ich), Paracetamol sei ein sanftes Lamm, nicht sehr kräftig, aber harmlos und trotzdem wirksam. Neue wissenschaftliche Daten sind geeignet, diesen Glauben zu erschüttern und das Paracetamol als Wolf im Schafspelz zu identifizieren. Ja, es scheint, als ob wir diesen Wolf nur sorgfältig "zerteilen" müssen, um die unschöne Wahrheit aus dem Bauch herauszuschälen. Es springen nämlich keine hübschen Geißlein heraus, sondern sieben hässliche Kröten. Viele Fachleute sind nicht mehr bereit, sie zu schlucken, und die Zweifel an diesem Wirkstoff nehmen zu [1]:

1. Leberschäden sind bei hoher Dosierung unvermeidlich. Sie kommen aber auch bei niedriger Dosierung vor [2; 3].

2. Die Entdeckung, dass Paracetamol ein präferentieller, nicht-selektiver Hemmer der Cyclooxygenase-2 ist [4], erklärt uns, warum bei kurzfristiger, mehr noch bei längerer Einnahme von Paracetamol der Blutdruck erhöht ist [5 – 7].

3. Ein länger bestehender, erhöhter Blutdruck und die Unterdrückung der Bildung des endothelialen Gefäßschutzwirkstoffes Prostacyclin erklären das vermehrte Auftreten von Herzinfarkten und Schlaganfällen [6; 8].

4. Die Kombination von Paracetamol mit einem nicht-selektiven Hemmer der Cyclooxygenase, wie z. B. Acetylsalicylsäure, führt besonders häufig zu Magen-Darm-Blutungen [9].

5. Hohe Paracetamolkonzentrationen nach oraler und parenteraler Applikation können zu Asthmaanfällen führen [10].

Diese "Kröten" könnte man mit dem Hinweis, es gibt kein Arzneimittel ohne Nebenwirkungen, abtun. Zwei neue Befunde sind aber besonders bedenklich, betreffen sie doch Schwangere und deren noch ungeborene Kinder sowie Kleinkinder:

6. Aus zwei großen skandinavischen, epidemiologischen Datenbankanalysen ergibt sich ein enger Zusammenhang mit einer verminderten männlichen Fertilität aufgrund von Hodenhochstand und reduzierter Hodenfunktion und der Einnahme von Paracetamol durch die Schwangere [11 – 12]. Die Ergebnisse von zwei unabhängigen Untersuchungen sollten uns nicht verwundern. Schließlich ist die Bedeutung des Prostaglandins bei der fetalen Entwicklung des Urogenitalsystems längst bekannt [13]. COX-2-Hemmer sind deswegen in der Schwangerschaft kontraindiziert.

7. Schließlich mehren sich die Arbeiten, die zeigen, dass Kinder häufiger an Asthma erkranken, wenn sie als Kleinkinder oder in der Gebärmutter Paracetamol ausgesetzt waren [14 – 18]. Ob diese immer noch umstrittene, aber durch zahlreiche Analysen nicht vom Tisch zu wischende Nebenwirkung von Paracetamol auf der Hemmung der Cyclooxygenasen in frühen Entwicklungsstadien zurückzuführen ist, ist zurzeit noch unklar. Schließlich kommt das Aspirin-induzierte Asthma bei den entsprechend empfindlichen Patienten durch Hemmung der Cyclooxygenase-1

zustande.

Fazit

Ist der Wolf im Schafspelz endlich als Wolf enttarnt, dürfen wir ihn nicht mehr frei herumlaufen lassen. Die bisher nicht bekannten Nebenwirkungen und Risiken des Paracetamols sollten Anlass sein zu überlegen, ob der rezeptfreie Zugriff auf Paracetamol, noch dazu in Kombinationspräparaten (z. B. Heißgetränken), noch zu vertreten ist. Während der Frühschwangerschaft ist die Anwendung nicht mehr zu rechtfertigen. Auch in späteren Schwangerschaftsphasen und beim Kleinkind ist eine Änderung des "Status" (rezeptfrei!) nötig. Viele unklare Todesfälle können auf den Gebrauch von Paracetamol zurückgeführt werden [19]. Leider glauben junge Frauen und werdende Mütter, in Form von Paracetamol einen milden, wirksamen, Vertrauen erweckenden, gut untersuchten, preiswerten Schmerz- und Fieberhemmstoff zu haben. Leider ist dem nicht so! Akute und chronische Schäden sind evident. Es ist daher an der Zeit, Paracetamol ganz vom Markt zu nehmen oder wenigstens das Prädikat "rezeptfrei" zu entziehen.

Prof. Dr. med. Dr. h.c. Kay Brune, Doerenkamp-Stiftungsprofessur für Innovationen im Tier- und Verbraucherschutz, Institut für Experimentelle und Klinische Pharmakologie und Toxikologie, Friedrich-Alexander-Universität Erlangen-Nürnberg

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Muss Paracetamol auf den Prüfstand?

Diskussion um neue Studien zu potenziellen Risiken von Paracetamol

Ginge es nach den Vorstellungen des Erlanger Pharmakologen Prof. Dr. Dr. Kay Brune, dann müssten Paracetamol-haltige Arzneimittel zumindest vollständig der Rezeptpflicht unterstellt werden, wenn nicht sogar ganz vom Markt genommen werden. In einem Gastkommentar in der DAZ (Nr. 49; S. 42 – 43) hatte er dies begründet. Wir wollten wissen, wie die Arzneimittelkommission der Deutschen Apotheker (AMK), das Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM) und der Bundesverband der Arzneimittelhersteller (BAH) die Situation einschätzen und haben gefragt, ob vor dem Hintergrund neuer Studien insbesondere zur Anwendung in der Schwangerschaft eine neue Nutzen-Risiko-Bewertung erforderlich ist.

In seinem Gastkommentar hatte Brune anhand der folgenden sieben Punkte erläutert, weshalb Paracetamol ein in seinen Augen kein harmloses Schmerz- und Fiebermittel ist:

1. Leberschäden sind bei hoher Dosierung unvermeidlich. Sie kommen aber auch bei niedriger Dosierung vor.

2. Die Entdeckung, dass Paracetamol ein präferentieller, nicht-selektiver Hemmer der Cyclooxygenase-2 ist, erklärt, warum bei kurzfristiger, mehr noch bei längerer Einnahme von Paracetamol der Blutdruck erhöht ist.

3. Ein länger bestehender, erhöhter Blutdruck und die Unterdrückung der Bildung des endothelialen Gefäßschutz-Wirkstoffes Prostacyclin erklären das vermehrte Auftreten von Herzinfarkten und Schlaganfällen.

4. Die Kombination von Paracetamol mit einem nicht-selektiven Hemmer der Cyclooxygenase, wie Acetylsalicylsäure, führt besonders häufig zu Magen-Darm-Blutungen.

5. Hohe Paracetamolkonzentrationen nach oraler und parenteraler Applikation können zu Asthmaanfällen führen.

6. Aus zwei großen skandinavischen, epidemiologischen Datenbankanalysen ergibt sich ein enger Zusammenhang mit einer verminderten männlichen Fertilität aufgrund von Hodenhochstand und reduzierter Hodenfunktion und der Einnahme von Paracetamol durch die Schwangere. Die Ergebnisse von zwei unabhängigen Untersuchungen sollten nicht verwundern. Schließlich sei die Bedeutung des Prostaglandins bei der fetalen Entwicklung des Urogenitalsystems längst bekannt, so Brune. COX-2-Hemmer sind deswegen in der Schwangerschaft kontraindiziert.

7. Schließlich würden sich die Arbeiten mehren, die zeigen, dass Kinder häufiger an Asthma erkranken, wenn sie als Kleinkinder oder in der Gebärmutter Paracetamol ausgesetzt waren. Ob diese immer noch umstrittene, aber durch zahlreiche Analysen nicht vom Tisch zu wischende Nebenwirkung von Paracetamol auf der Hemmung der Cyclooxygenasen in frühen Entwicklungsstadien zurückzuführen ist, ist nach Ansicht von Brune zurzeit noch unklar. Schließlich würde das Aspirin-induzierte Asthma bei den entsprechend empfindlichen Patienten durch Hemmung der Cyclooxygenase-1 zustande kommen.

BfArM: Neue Risikosignale werden bewertet

Dazu merkt das BfArM an, dass die unter den Punkten 1 bis 5 genannten Nebenwirkungen und Risiken bekannt seien. Sie seien jedoch in erster Linie bei hohen Dosierungen oder Überdosierungen, Missachtung von Kontraindikationen oder längerer Einnahmedauer zu erwarten. In den Gebrauchsinformationen von OTC-Arzneimitteln mit Paracetamol würden sich entsprechende Hinweise zu Dosierung, Kontraindikationen und Einnahmedauer ohne ärztliche Kontrolle finden.

Die Frage der Verschreibungspflicht und einer Begrenzung der Packungsgröße sei im Jahr 2008 vom Sachverständigenausschuss für Verschreibungspflicht behandelt worden. Dessen Empfehlung habe zu einer Begrenzung der nicht verschreibungspflichtigen Packungsgrößen geführt: Packungen mit mehr als 10 g Paracetamol seien der Verschreibungspflicht unterstellt worden.

Die angesprochenen neuen Signale für die Risiken Kryptorchismus oder Asthma bei Kindern, deren Mütter in der Schwangerschaft Paracetamol einnahmen oder als Kleinkinder mit Paracetamol behandelt wurden, werden zurzeit unter Mitwirkung des BfArM von der Pharmakovigilanz-Arbeitsgruppe (PhVWP) des Ausschusses für Humanarzneimittel (CHMP) der Europäischen Arzneimittelagentur (EMA) bewertet. Wenn sich aus dieser Bewertung Empfehlungen für risikomindernde Maßnahmen ergeben werden, so das BfArM, werden diese auch in Deutschland umgesetzt werden.

AMK: kein Anlass für Neubewertung

Die Arzneimittelkommission der Deutschen Apotheker (AMK) hatte vor Kurzem zusammen mit der Deutschen Pharmazeutischen Gesellschaft (DPhG) eine Stellungnahme zur Risikominimierung durch rationalen Einsatz nicht-opioider Analgetika in der Selbstmedikation herausgegeben. AMK und DPhG betonen darin, dass Paracetamol größere Risiken berge als bislang angenommen (s. Kasten).

AMK/DPhG-Stellungnahme zu Paracetamol

Auszug aus der AMK/DPhG-Stellungnahme zur Risikominimierung durch rationalen Einsatz nicht-opioider Analgetika in der Selbstmedikation
(DAZ 2010; Nr. 48, S. 26 – 28):

... Auch Paracetamol birgt größere Risiken als lange Zeit angenommen. Wenngleich der Arzneistoff bei bestimmungsgemäßer Kurzzeitgabe (bis maximal 4 g pro Tag über maximal 3 bis 4 Tage) nur eine geringe Rate an UAW aufweist und in der Pädiatrie, bei Schwangeren sowie bei Patienten mit gastrointestinalen Ulzerationen in der Anamnese eingesetzt werden kann, liegt ein bedeutender Nachteil in der geringen therapeutischen Breite: Schon ab einer dauerhaften Einnahme von 7,5 g täglich können sich bei Erwachsenen Leberzellnekrosen entwickeln [7, 8]. Ähnlich wirken einmalige Dosen ab 10 bis 12 g [7, 8]. Bei vorgeschädigter Leber, Einnahme weiterer hepatotoxischer Substanzen oder Induktoren des Cytochrom-P-450-Systems muss zudem mit niedrigeren Schwellendosen gerechnet werden. Wird nicht rechtzeitig das Antidot Acetylcystein gegeben, entwickelt sich ein Coma hepaticum, das unbehandelt zum Tod führt.

Das Risiko eines unsachgemäßen Einsatzes von Paracetamol wird durch die 4184 Giftberatungsfälle deutlich, die im Jahre 2006 in den deutschen Giftinformationszentren zu diesem Analgetikum registriert wurden. Hierbei handelte es sich zu 63 Prozent um Suizidversuche [9]. Neben beabsichtigten spielen aber auch akzidentelle Intoxikationen eine Rolle, zum Beispiel als Folge der zeitgleichen Anwendung mehrerer Paracetamol-haltiger Fertigarzneimittel wie Tabletten, Suppositorien und (Kombinations-)Arzneimitteln für die Behandlung von Erkältungskrankheiten (u. a. so genannte Heißgetränke). Da hierbei nicht selten supratherapeutische Dosen wiederholt über mehrere Tage eingenommen werden, kann es schon bei tieferen Dosen als bei der akuten einmaligen Überdosierung zu einer Leberschädigung kommen. In den USA sterben jährlich 500 Patienten an den Folgen einer Überdosierung mit diesem Analgetikum/Antipyretikum (10). Für Deutschland sind hierzu keine genauen Zahlen bekannt.

Auf weitere Risiken von Paracetamol bei Langzeittherapie weisen neuere Untersuchungen hin: Da Paracetamol die COX-2 hemmt [11], wird zunehmend eine kritische Analyse seines kardiovaskulären Risikopotenzials durch randomisierte klinische Studien gefordert [4, 5]. Erste prospektive Kohortenstudien weisen der langfristigen und häufigen Einnahme von Paracetamol eine den nicht steroidalen Antiphlogistika vergleichbare Blutdruckerhöhung und Rate unerwünschter kardiovaskulärer Ereignisse zu [12, 13]. Zudem scheint epidemiologischen Studien zufolge die langfristige kombinierte Gabe von nicht steroidalen Antiphlogistika und Paracetamol das Risiko gastrointestinaler UAW überadditiv zu erhöhen [14, 15]. ...

Die Unterstellung von Paracetamol unter die Verschreibungspflicht in Packungen mit mehr als 10 g wird daher uneingeschränkt befürwortet. Weitere Maßnahmen werden nicht gefordert. Im Hinblick auf die Anwendung in der Schwangerschaft sieht die AMK derzeit keinen Anlass zu einer Neubewertung der zulassungskonformen Anwendung, so Prof. Dr. Martin Schulz, Vorsitzender der AMK gegenüber der DAZ. Er beruft sich in diesem Punkt auf die Ausführungen des Pharmakovigilanz- und Beratungszentrum für Embryonaltoxikologie (http://www.embryotox.de/paracetamol.html). Dort heißt es:

> Planung einer Therapie oder Planung einer Schwangerschaft unter Therapie: Paracetamol ist das Analgetikum und Antipyretikum der Wahl. Es kann in jeder Phase der Schwangerschaft innerhalb des üblichen Dosisbereichs eingesetzt werden.
>
> Konsequenzen nach Anwendung in der Schwangerschaft: keine.
>
> Besser erprobte Alternativen: keine.

Diesen Ausführungen habe die AMK nichts hinzuzufügen, so Schulz.

BAH: Keine Rechtfertigung für Marktrücknahme

Für den Bundesverband der Arzneimittelhersteller (BAH) ergeben sich bei näherem Hinsehen aus den von Brune zitierten Arbeiten keine Hinweise auf neue Risiken, die es rechtfertigen würden, Paracetamol-haltige Arzneimittel insgesamt der Verschreibungspflicht zu unterstellen oder vom Markt zu nehmen (s. Stellungnahme).

BAH-Stellungnahme:
"Unterstellung unter Verschreibungspflicht nicht gerechtfertigt!"

In seinem Gastkommentar "Paracetamol – ein Wolf im Schafspelz läuft frei herum!" (DAZ 2010, Nr. 49, S. 42 – 43) nimmt Professor Brune neuere Publikationen zu möglichen Auswirkungen von Paracetamol in der Schwangerschaft zum Anlass, die Datenlage von Paracetamol "noch einmal genauer anzuschauen".

Brune führt insgesamt 19 Literaturstudien an, die seiner Meinung nach eine Neubewertung des Nutzens und der Risiken von Paracetamol erforderlich machen. Im Rahmen dieser Stellungnahme können selbstverständlich nicht alle Artikel und die darin diskutierten Studien erläutert werden. Viele der zitierten Studien weisen methodische Schwächen oder andere Mängel auf; einige der zitierten Arbeiten enthalten überhaupt keine Daten zu Paracetamol, sondern fassen andere – ebenfalls zitierte – Arbeiten nur erneut zusammen. So stellt die Arbeit von White und Campbell [Zitat 7] lediglich ein Editorial zu Forman et al. [Zitat 6] dar. Die im Zusammenhang mit dem dritten Vorwurf – vermehrtes Auftreten von Herzinfarkten und Schlaganfällen unter Paracetamol – zitierte Arbeit von Forman et al. [Zitat 6] untersuchte erst gar nicht die Assoziation einer Paracetamol-Einnahme mit Herzinfarkten und Schlaganfällen; die daraus abgeleiteten Empfehlungen können daher auch nicht einen solchen Zusammenhang belegen. Die Arbeit von Chan et al. [Zitat 8], die eine Kohorte US-amerikanischer Krankenschwestern über zwölf Jahre lang befragt hat, fand eine Assoziation einer NSAIDs-Einnahme und dem erhöhen Risiko kardiovaskulärer Ereignisse erst dann, wenn das Arzneimittel an mehr als an 22 Tagen pro Monat eingenommen wurde. Eine solche Dauereinnahme fällt zweifelsohne nicht in den Anwendungsbereich rezeptfreier Analgetika und kann daher auch nicht herangezogen werden, um zu begründen, dass verschreibungsfreie Produkte der Rezeptpflicht unterstellt werden sollen.

Diese Reihe methodischer Schwächen könnte weiter fortgeführt werden. Dass dies nicht notwendig ist, lässt sich auch aus der Arbeit von Brune ableiten, der im Wesentlichen seine Forderung nach einer Neubewertung von Paracetamol nicht aus den ersten fünf, sondern aus den letzten beiden Punkten ableitet, also einer vermuteten verminderten Fertilität männlicher Kinder (Kryptorchismus) und einem erhöhten Asthma-Risiko während der Schwangerschaft bzw. bei Kleinkindern.

Die erstgenannte Behauptung stützt sich auf zwei Publikationen zu epidemiologischen Studien (Jensen et al. [Zitat 11] und Kristensen et al. [Zitat 12]). Jensen et al. fanden jedoch allenfalls sehr schwache Korrelationen zwischen einer Paracetamol-Einnahme während der Schwangerschaft über mehr als vier Wochen und einer verminderten Fertilität. Nahezu alle erfassten Parameter waren schlussendlich statistisch nicht signifikant (die 95% Konfidenzintervalle der hazard ratios schließen 1.0 ein). Bei einem einzigen Parameter (Paracetamol-Einnahme länger als vier Wochen während der Schwangerschaft) fand sich ein gerade eben statistisch signifikantes Ergebnis (95% CI: 1.05-1.83). Zudem hat diese Untersuchung die inhärenten Beschränkungen epidemiologischer Studien (wie z.B. unberücksichtigte confounding factors, recall bias, statistische Bewertung multipler Vergleiche). Kristensen et al. untersuchten die Assoziation zwischen der Einnahme leichter Analgetika während der Schwangerschaft und Kryptorchismus bei dänischen und finnischen Frauen. Eine Paracetamol-Einnahme war in keiner der Kohorten mit einem signifikanten Anstieg der Häufigkeit von Kryptorchismus korreliert.

Beide Publikationen belegen somit nicht das Risiko für Kryptorchismus durch eine Paracetamol-Einnahme der Mutter während der Schwangerschaft.

Bleibt nur noch der siebte Punkt, der Verdacht eines erhöhten Asthma-Risikos bei Einnahme von Paracetamol während der Schwangerschaft, bzw. bei Kleinkindern.

Die diesbezüglich angeführten Publikationen sind entweder epidemiologische Studien [Zitate 16, 17, 18] oder eine Metaanalyse epidemiologischer Studien [Zitat 14]. In dem von Brune selbst zitierten kritischen Review [Zitat 15] bemängeln Scialli et al. die Restriktionen der Aussagekraft sowie die Qualität der vorhandenen epidemiologischen Studien und kommen dabei zur Schlussfolgerung, dass die vorliegenden Daten insuffizient seien, um ein Risiko durch Paracetamol zu zeigen.

Schließlich weist Brune in seinem Fazit noch auf die Publikation von Marinetti et al. [Zitat 19] hin. In dieser Arbeit wurden zehn Todesfälle bei Kleinkindern vorgestellt, die z.T. Paracetamol-haltige Präparate erhalten hatten. In einem Fall (Paracetamol-Plasmaspiegel 117 mg/l) wurde als Todesursache Sepsis aufgrund einer Pneumonie diagnostiziert, wobei Paracetamol als verstärkender Faktor benannt wurde, also auch nicht als eigentliche Todesursache. In allen anderen Fällen wurden andere Todesursachen diagnostiziert bzw. traten keine Paracetamol-typischen Intoxikationserscheinungen auf. Auch diese Arbeit (die zudem schon 2005 erschienen ist) liefert somit keine Hinweise auf neue, bisher unbekannte Paracetamol-Risiken.

Fazit

Bei näherem Hinsehen ergeben sich aus den von Prof. Brune zitierten Arbeiten keine Hinweise auf neue Risiken, die es rechtfertigen würden, Paracetamol-haltige Arzneimittel insgesamt der Verschreibungspflicht zu unterstellen oder gar ganz vom Markt zu nehmen. In therapeutischen Dosierungen verwendet ist Paracetamol ein bewährter und sicherer Wirkstoff in der Selbstmedikation. Um Risiken im Zusammenhang mit den bekannten hepatotoxischen Wirkungen von Paracetamol bei erheblicher Überdosierung zu reduzieren, wurde die verschreibungsfrei erhältliche Packungsgröße bereits erheblich reduziert.

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du

Acetaminophen Increases Blood Pressure in Patients With Coronary Artery Disease

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Background—Because traditional nonsteroidal antiinflammatory drugs are associated with increased risk for acute cardiovascular events, current guidelines recommend acetaminophen as the first-line analgesic of choice on the assumption of its greater cardiovascular safety. Data from randomized clinical trials prospectively addressing cardiovascular safety of acetaminophen, however, are still lacking, particularly in patients at increased cardiovascular risk. Hence, the aim of this study was to evaluate the safety of acetaminophen in patients with coronary artery disease.

Methods and Results—The 33 patients with coronary artery disease included in this randomized, double-blind, placebo-controlled, crossover study received acetaminophen (1 g TID) on top of standard cardiovascular therapy for 2 weeks. Ambulatory blood pressure, heart rate, endothelium-dependent and -independent vasodilatation, platelet function, endothelial progenitor cells, markers of the renin-angiotensin system, inflammation, and oxidative stress were determined at baseline and after each treatment period. Treatment with acetaminophen resulted in a significant increase in mean systolic (from 122.4±11.9 to 125.3±12.0 mm Hg $P=0.02$ versus placebo) and diastolic (from 73.2±6.9 to 75.4±7.9 mm Hg $P=0.02$ versus placebo) ambulatory blood pressures. On the other hand, heart rate, endothelial function, early endothelial progenitor cells, and platelet function did not change.

Conclusions—This study demonstrates for the first time that acetaminophen induces a significant increase in ambulatory blood pressure in patients with coronary artery disease. Thus, the use of acetaminophen should be evaluated as rigorously as traditional nonsteroidal antiinflammatory drugs and cyclooxygenase-2 inhibitors, particularly in patients at increased cardiovascular risk.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00534651.

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Key Words: acetaminophen ■ blood pressure ■ coronary disease ■ endothelium

The Food and Drug Administration has mandated a "black-box warning" for cyclooxygenase-2 (COX-2) selective inhibitors and nonselective nonsteroidal antiinflammatory drugs (NSAIDs) in view of the potential of these agents to increase adverse cardiovascular outcomes.[1] Whereas hundreds of millions of patients worldwide continue to require pain-relieving therapy to maintain an acceptable quality of life, the uncertainty around the cardiovascular safety of NSAIDs and COX-2 inhibitors leaves practitioners and patients with difficult management decisions. Current guidelines recommend acetaminophen as the first-line analgesic of choice for the management of chronic pain despite weaker analgesic potency on the assumption of its greater cardiovascular safety, particularly in patients at high cardiovascular risk or with established cardiovascular disease.[1]

Editorial see p 1779
Clinical Perspective on p 1796

One of the most commonly used drugs worldwide, a major ingredient in numerous cold and flu medications, and a drug commonly used even in children and pregnant women, acetaminophen (known as paracetamol outside the United

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States) was hitherto considered safe when taken in therapeutic doses.[1,2] It is of note, however, that sporadic studies linked acetaminophen with a higher incidence of hypertension[3,4] or even increased risk for cardiovascular events.[5] Only a few interventional studies assessing the effect of acetaminophen on hypertension are available, and all of them were performed either in hypertensive patients[6,7] or in patients who were hypertensive with osteoarthritis.[8] The results, however, are inconsistent. Nevertheless, the majority of data on the cardiovascular safety of acetaminophen are derived from observational studies, which are considered "hypothesis generating," and many examples exist where such findings were not confirmed in randomized trials.[6–8]

To date, no study has assessed the effect of acetaminophen on blood pressure (BP) in patients with coronary artery disease (CAD). Thus, we prospectively evaluated the potential impact of acetaminophen on ambulatory BP (ABP) and vascular function in patients with established CAD in whom traditional NSAIDs and COX-2 inhibitors are contraindicated and acetaminophen currently represents the treatment of choice.

Methods

Study Population

The patients were recruited at the Cardiovascular Center Cardiology, University Hospital Zurich, Zurich, Switzerland. Patients with CAD (documented by coronary angiography, nuclear imaging, or positive stress test) on stable cardiovascular medication for at least 1 month who were between 18 to 80 years of age and gave written informed consent were included in the study.

Exclusion criteria were acute myocardial infarction, unstable angina, stroke, or coronary intervention/revascularization procedure within 3 months before study entry; left ventricular ejection fraction <50%; use of other analgesics (platelet inhibition therapy with aspirin 100 mg/d was continued); chronic pain; smoking, alcohol, or substance abuse; uncontrolled BP despite adequate therapy (>160/100 mm Hg); renal failure (serum creatinine >200 μmol/L); liver disease (alanine aminotransferase or aspartate aminotransferase >100 IU); acute hepatitis; hyperbilirubinemia; concomitant therapy with oral anticoagulants, Phenobarbital, phenytoin, carbamazepine, isonicotinic acid, chloramphenicol, chlorzoxazone, zidovudine, and salicylamide; long-term use of nitrates; insulin-dependent diabetes mellitus; anemia (hemoglobin <10 g/dL); known allergies to acetaminophen; systemic inflammatory diseases (eg, rheumatoid arthritis, Crohn's Disease); and participation in another study within the last month. The patients were not allowed to take any drugs other than the background cardiovascular therapy (in particular, no anti-inflammatory and pain-relieving drugs) to secure the double-blind design.

Because patients included in the study did not present with pain and thus would potentially not benefit from the study drug, the number of patients investigated had to be limited to the minimal number determined by a preliminary power calculation. In addition, to limit the number of patients to exposure to a drug from which they potentially would not benefit, a "crossover" design was chosen.

Study Design and Protocol

In this prospective randomized, double-blind, investigator-initiated crossover study, we analyzed the impact of acetaminophen on ABP and endothelium-dependent and -independent vasodilatation in patients with stable CAD receiving optimal standard treatment. As secondary end points, platelet function, endothelial progenitor cells (EPCs), markers of the renin-angiotensin system, inflammation, and oxidative stress were assessed.

After screening and recruiting, the patients were randomly assigned to 2 groups. For randomization, an unpredictable allocation sequence was provided by external institutions (InterCorNet and Cantonal Pharmacy, both in Zurich, Switzerland), which were responsible for the blinding and labeling of the drugs. All investigators were unaware of the allocation procedure at any time. The patients were randomized to receive either acetaminophen 1 g TID, a typical dose for pain relief, or matching placebo for 2 weeks in the first part of the study or vice versa in the second part. Between the first and the second parts was a washout period of 2 weeks.

At each visit (baseline and after 2, 4, and 6 weeks), ABP and endothelial function were measured, blood samples were drawn, 24-hour urine was collected, clinical status was assessed, and adverse events were recorded. At each visit, a safety analysis was performed, including the assessment of electrolytes and of liver and kidney function, plus a white and red blood cell count. Pregnancy testing in women with child-bearing potential was performed only at the first visit. The patients were advised not to take their usual drugs in the morning of the examination day (all examinations and measurements were performed in the morning). Blood samples were taken and flow-mediated dilatation (FMD) was assessed before the patients took their medications. The regular medications and study drug were taken thereafter and before the 24-hour ABPM was placed.

The study drug and placebo were prepared in identical capsules to ensure uniform appearance of both formulations. The verum consisted of pure acetaminophen and did not contain sodium, with the exception of a 3% solution containing sodium lactate on the capsule surface. According to the manufacturer, this amount of sodium is not measurable in vivo. The placebo preparation contained D-mannitol only. The Ethics Committee of the Canton Zurich and the Swiss Agency for Therapeutic Products (Swissmedic) approved the study protocol. The study was registered at http://www.clinicaltrials.gov (identifier: NCT00534651).

ABP Measurement

ABP measurements were obtained over 24 hours with the Tracker NIBP 2 (Delmar, Del Mar Reynolds Medical, Hertford, UK) before and after the active treatment phase according to recent guidelines.[9] Patients were asked to keep their arm calm while the cuff was inflating and to avoid excessive physical exertion during monitoring. The monitors were programmed to take readings every 15 minutes during daytime and every 30 minutes during nighttime.

Endothelium-Dependent and -Independent Vasodilatation

FMD was performed according to current guidelines[10,11] as previously described.[12] In brief, a B-mode scan of the left brachial artery was obtained in a longitudinal section between 2 and 10 cm above the elbow with a high-resolution 10-MHz linear-array transducer and a high-resolution ultrasound system (Siemens X300, Siemens Switzerland AG, Zurich, Switzerland). The analog video signal was acquired with a video processing system that computed the artery diameter in real time (FMD Studio,[13,14] a system for real-time measurement, Institute of Clinical Physiology, Pisa, Italy). The reproducibility of the method has been demonstrated recently.[13,14] Baseline vessel size was considered to be the mean of the measures obtained during the first minute. FMD was calculated as the maximal percent increase in diameter above baseline. Endothelium-independent dilatation was measured after sublingual glycerol trinitrate (0.4 mg, Nitrolingual Spray, Pohl-Boskamp, Hohenlockstedt, Germany) application by recording arterial diameter continuously for at least 6 minutes. The response to glycerol trinitrate is calculated as the maximum percent increase in vessel size above the baseline.

The intraobserver mean of absolute difference in baseline diameter was 0.13±0.09 (I.S.) and 0.11±0.06 (P.K.), and the mean absolute difference in FMD was 0.61±0.19% (I.S.) and 0.62±0.46% (P.K.). The intraobserver coefficient of variation (CV) of the operators (defined as follows: SD of the paired differences/overall mean/$\sqrt{2}\times 100$) was 2.1% (I.S.) and 6.2% (P.K.).

Special Laboratory Analysis

Oxidative Stress Markers

8-Isoprostanes were measured in the plasma with an 8-isoprostane enzyme immunoassay (Cayman Chemicals, Ann Arbor, Mich; intra-assay CV, 7.2%; interassay CV, 15.5%).

Prostaglandins and Thromboxane

Prostaglandin E_2 was measured in plasma and urine with the prostaglandin E_2 enzyme immunoassay kit–monoclonal (Cayman Chemicals; intra-assay CV, 3.7%; interassay CV, 11.6%). Thromboxane B_2 was determined in plasma with the thromboxane B_2 enzyme immunoassay kit (Cayman Chemicals; intra-assay CV, 19.9%; interassay CV, 24.3%).

Assessment of Plasma Renin Activity and Aldosterone

Plasma renin activity was measured by trapping generated angiotensin I by high-affinity antibodies and subsequent radioimmunoassay.[15] Aldosterone was measured by a direct radioimmunoassay with high-affinity antibodies produced in New Zealand White rabbits.[16] For aldosterone, the intra-assay and interassay CVs were 5.3% and 9.4%. For plasma renin activity, the intra-assay and interassay CVs were 5% and 13%. The results were normalized to 24-hour sodium excretion.

Early EPCs

Isolation and Culturing of Early EPCs From Peripheral Blood

Blood (8 mL) was collected into BD Vacutainer Cell Preparation Tubes (BD, Franklin Lakes, NJ) and was centrifuged at 1800 *g* for 30 minutes at room temperature within 1 to 2 hours. The plasma layer was removed and stored at −80°C; the buffy layer was transferred to sterile 15-mL centrifuge tubes. Mononuclear cells were washed twice with PBS, first with 15 mL and spin at 900*g* for 15 minutes and then with 10 mL and spin at 900*g* for 10 minutes, and seeded on a fibronectin-coated Laboratory Tek Chamber Slide (BD) at a density of 8 000 000/mL in 20% FCS EGM-2. After 3 days, the medium was changed. The cultures were analyzed on the fifth day of plating.

Quantification and Characterization of Early EPCs in 5-Day Cultures

Early EPCs were quantified as described in detail previously.[17,18] In brief, the medium was removed with pipette, and EGM-2 with 5 μg/mL 1,1-dioctadecyl-3,3,3-tetramethylindocarbocyanine perchlorate low-density lipoprotein (DiI-LDL; Intracel, Frederick, MD) was added. The cells were incubated with DiI-LDL for 1 hour at 37°C. Then cells were washed with PBS and fixed with 4% paraformaldehyde in PBS for 10 minutes at room temperature. After removal of paraformaldehyde, cells were washed once with PBS and incubated with 10 μg/mL FITC-conjugated agglutinin lectin from *Ulex europaeus* (Sigma-Aldrich, Buchs, Switzerland) for 1 hour at room temperature. Then they were washed twice and covered by mounting medium with DAPI (1:1000). Using a fluorescent microscope (Olympus, Hamburg, Germany), we counted DiI-LDL/lectin double-positive cells in 3 different visual fields and considered them early EPCs. The CV was 6.3% (10 EPC cultures made twice). Furthermore, the number of CD34/KDR double-positive mononuclear cells was determined by fluorescence-activated cell sorting analysis.

Shear Stress–Dependent Platelet Function

Shear stress–dependent platelet function was assessed with a cone and platelet analyzer as described.[19]

Statistical Analysis

The primary end points were the changes in mean 24-hour systolic ABP (SBP) and diastolic ABP (DBP) and the change in FMD after 2 weeks of treatment with acetaminophen compared with placebo. After evaluation of the first 22 patients, the analysis demonstrated insufficient power for the results on BP measurements. Therefore, using the data obtained so far (SD of the difference, 4.9 mm Hg; minimal detectable difference in means, 2.5 mm Hg), we calculated the sample size needed (33 patients) for an 81% statistical power and a significance level of 0.05 (2 sided) for this crossover study. Analysis was performed with Wilcoxon-Mann-Whitney *U* tests (to account for possible nonnormality of the end points) using methods discussed by Senn.[20] That is, we considered 2 distinct groups of patients: group 1, who received acetaminophen followed by placebo, and group 2, who received placebo followed by acetaminophen. Within each group, data are summarized by examining within-patient changes between periods 1 and 2 (For both groups, this is a subject's respective change from baseline while on acetaminophen minus the change from baseline while on placebo). These unpaired change scores are then analyzed across groups 1 and 2 with the Wilcoxon rank-sum test (Mann-Whitney *U* test), as proposed by Hill and Armitage[21] and later discussed by Senn.[20] The effect of acetaminophen is estimated as the average of the 2 group-specific mean change scores. The period effect is estimated using the difference of the 2 group-specific mean change scores (divided by 2). The carryover effect was excluded through the use of an unpaired Wilcoxon test of within-patient change from baseline including only the first period of treatment. Because there were 3 end points of primary interest, a Bonferroni correction was made. Results are presented as mean±SD or SEM as described.

Analysis of the primary end point was performed in the R programming language (R Development Core Team, 2009). The statistical software package SPSS 17 (SPSS Inc, Chicago, Ill) was used to evaluate differences in the clinical characteristics. Statistical significance was accepted at $P<0.05$.

Results

Study Population

A total of 37 patients were enrolled; however, 4 patients withdrew their informed consent because of personal reasons after the first visit (Figure 1). Therefore, 33 patients (mean age, 60.5±8.5 years; 28 men; body mass index, 27.8±6.0 kg/m^2) were included in the analysis. Their clinical characteristics and baseline laboratory are presented in Tables 1 and 2.

Effects of Acetaminophen on 24-Hour BP

Acetaminophen (1 g TID) induced a significant increase in SBP (from 122.4±11.9 to 125.3±12.0 mm Hg; $P=0.021$ compared with placebo) and DBP (from 73.2±6.9 to 75.4±7.9 mm Hg; $P=0.024$ compared with placebo), whereas there was no change after placebo (SBP, from 122.7±11.6 to 122.2±10.5 mm Hg; DBP, from 74.4±6.9 to 74.6±7.2 mm Hg; Figure 2 and Table 1).

Heart rate in the 24-hour measurement increased with acetaminophen (from 68.2±10.2 to 70.8±10.1 bpm) and did not change with placebo (from 68.7±9.7 to 67.9±8.1 bpm). There was no significant difference between acetaminophen and placebo ($P=0.22$; Table 1).

A period effect was excluded for 24-hour SBP, DBP, and heart rate ($P=0.62$, 0.59, and 0.32, respectively). A carryover effect was excluded for 24-hour SBP, DBP, and heart rate ($P=0.67$, 0.53, and 0.41, respectively).

Effects of Acetaminophen on Endothelium-Dependent and -Independent Vasodilatation

After 2 weeks of treatment with acetaminophen, there was no change in FMD compared with placebo (from 4.73±2.3% to 4.53±2.22% and from 4.68±2.54% to 4.71±2.15%; $P=0.64$; Table 1). Endothelium-independent vasodilatation, as assessed with glycerol trinitrate, remained unaltered (from 13.9±6.0% to 13.4±5.1% with acetaminophen and from

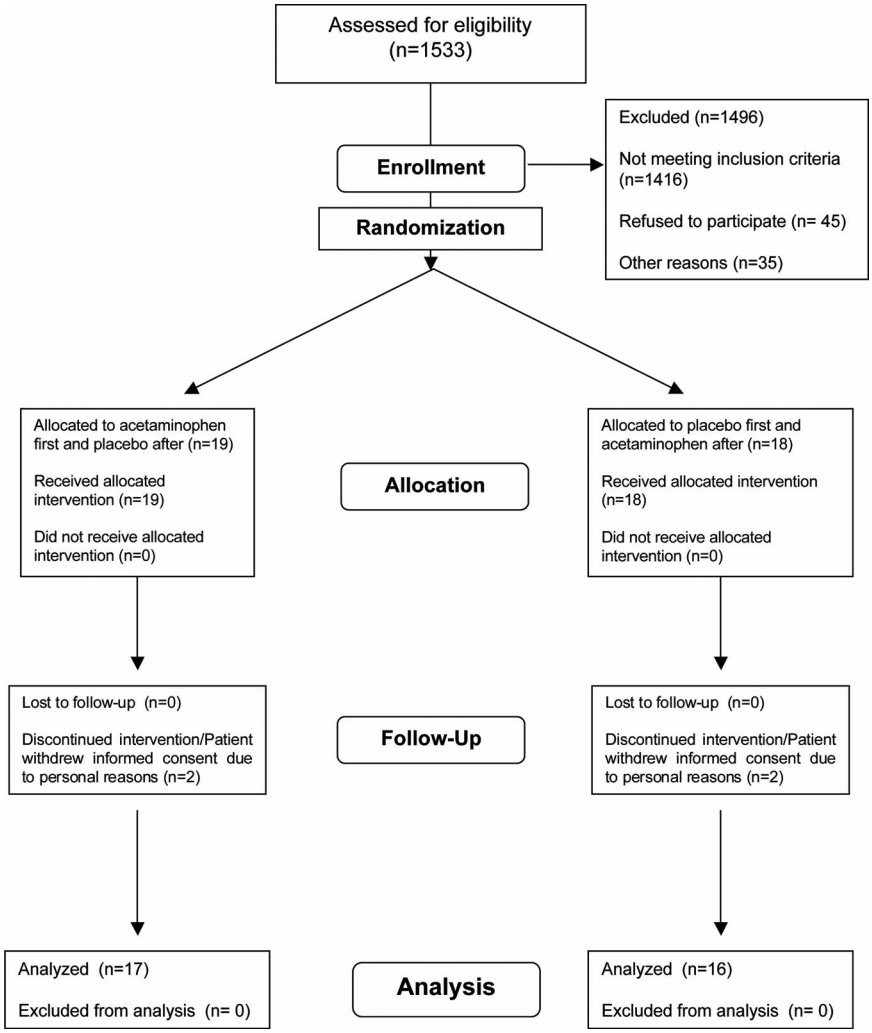

Figure 1. Flow chart of the study.

13.7±5.2% to 14.0±7.0% with placebo; $P=0.66$; Table 1). Baseline diameters (before acetaminophen, 4.45±0.65 mm; after acetaminophen, 4.46±0.58 mm; before placebo, 4.36±0.61 mm; and after placebo, 4.35±0.61 mm; $P=0.64$) and percent changes in flow velocity (before acetaminophen, 196.2%; after acetaminophen, 193.1%; before placebo, 203.1%; and after placebo, 201.5%; $P=0.92$) were similar in the 2 groups.

Effect of Acetaminophen on EPCs

The proportion of EPCs (percent double positive for both CD34 and CD309) was evaluated in 22 of the 33 patients and did not differ 2 weeks after treatment with acetaminophen or placebo (0.23% versus 0.34%, respectively; $P=0.11$).

Effect of Acetaminophen on Platelet Adhesion

Two weeks of treatment with acetaminophen 1 g TID or placebo did not change platelet adhesion significantly (area fraction, from 3.1±1.5% to 3.9±2.5% with acetaminophen and from 3.4±1.6% to 4.3±1.5% with placebo; $P=0.34$; Table 2).

Effect of Acetaminophen on Laboratory Parameters

Laboratory parameters before and after acetaminophen and placebo are shown in Table 2. No significant change in laboratory parameters was seen with the exception of γ-glutamyltransferase in the active treatment group. One patient showed a significant increase in γ-glutamyltransferase during acetaminophen therapy without any changes in alanine and aspartate aminotransferase; γ-glutamyltransferase normalized 2 weeks after cessation of the administration of acetaminophen. This patient denied recreational use of alcohol during the study time. The participant was included in the data analysis.

Discussion

This study demonstrates for the first time a significant increase in ABP in patients with CAD treated with acetaminophen but no significant effect on endothelial function, EPCs, or platelet function.

Selective and nonselective NSAIDs are associated with an increased risk for cardiovascular events.[22] Thus, current guidelines suggest avoiding NSAIDs and COX-2 inhibitors in patients with high cardiovascular risk or established CAD[1] and recommend acetaminophen as the first-line analgesic of choice, particularly in patients with high cardiovascular risk. The results of the present study, however, question the assumption of the cardiovascular safety of acetaminophen because they provide the first prospective evidence that

Table 1. Clinical Measures Before and After Acetaminophen, Placebo, and Concomitant Drug Therapies During the Whole Study

	Baseline for Treatment Period	Acetaminophen	Baseline for Control Period	Placebo
Clinical parameters				
FMD, %	4.73±2.30	4.53±2.22	4.68±2.54	4.71±2.15
GTN, %	13.9±6.0	13.4±5.1	13.7±5.2	14.0±7.0
24-h SBP, mm Hg	122.4±11.9	125.3±12.0*	122.7±11.6	122.2±10.5
Daytime SBP, mm Hg	124.5±12.2	127.3±12.5*	125.2±12.2	124.2±10.7
Nighttime SBP, mm Hg	115.7±12.4	117.7±12.4	114.1±1094	114.7±12.4
24-h DBP, mm Hg	73.2±6.9	75.4±7.9*	74.4±6.9	74.6±7.2
Daytime DBP, mm Hg	75.1±7.4	76.9±8.6*	76.2±7.7	76.1±7.7
Nighttime DBP, mm Hg	66.9±7.3	68.5±7.8	67.4±7.1	66.9.0±6.4
24-h HR, bpm	68.2±10.3	70.8±10.1*	68.7±9.7	67.9±8.1
Daytime HR, bpm	69.8±10.5	72.4±9.8*	70.9±9.5	70.9±9.0
Nighttime HR, bpm	62.1±8.4	64.6±10.2*	63.6±9.3	64.1±9.2
Office SBP, mm Hg	131.5±15.8	133.8±16.2	131.8±11.5	130.6±10.6
Office DBP, mm Hg	80.6±8.8	82.7±8.7	81.0±6.8	81.3±8.7
Office HR, bpm	58.6±7.5	60.2±7.5	59.9±10.2	60.0±8.0
Body weight, kg	84.3±17.3	84.4±17.6	84.4±17.3	84.7±17.5
Concomitant medication, n (%)				
ACE inhibitor	21/33 (64)			
ARB	7/33 (21)			
β-blocker	17/33 (52)			
Calcium antagonist	6/33 (18)			
Aspirin (100 mg)	31/33 (94)			
Clopidogrel	11/33 (33)			
Statin	30/33 (91)			
Ezetimibe	2/33 (6)			

GTN indicates glycerol trinitrate; HR, heart rate; ACE, angiotensin-converting enzyme; DBP, diastolic blood pressure; SBP, systolic blood pressure; and ARB, angiotensin receptor blocker. Data are shown as mean±SD.

*Statistically significant difference ($P<0.05$), acetaminophen versus placebo.

acetaminophen increases ambulatory BP in patients with CAD. Importantly, the observed increase in BP associated with the use of acetaminophen was within the range of the hypertensive effects of traditional NSAIDs, particularly diclofenac and ibuprofen.[3,23–30] Importantly, epidemiological studies such as that by Forman and coworkers[3] demonstrated that men who took acetaminophen 6 to 7 d/wk compared with nonusers demonstrated an increased relative risk for incident hypertension compared with those taking NSAIDs. Additionally, in the Nurses' Health Study I and II, the multivariable-adjusted relative risk of incident hypertension for women who took acetaminophen >500 mg/d was increased almost 2-fold compared with women who did not use acetaminophen.[25] Although the most rigorous way to examine an association between nonnarcotic analgesics and hypertension would be a randomized controlled trial,[31] such a trial randomizing patients with chronic pain to analgesics versus placebo is ethically questionable and unlikely to be performed.

Prospective controlled studies with acetaminophen are scarce, and the results inconsistent.[6–8] Indeed, 1 study showed a 4-mm Hg increase[6] and the remaining 2 showed no change in BP associated with the use of acetaminophen in patients with hypertension.[7,8] It is of note that these studies were performed in patients with hypertension, not in the high-risk group of patients with established CAD in whom the use of acetaminophen is recommended by current guidelines.[6–8]

Because the use of acetaminophen is prevalent, the pressor response found in our study is a major public health concern. Indeed, in view of the established continuous incremental risk of cardiovascular and cerebrovascular disease in relation to BP, an increase in BP associated with the use of acetaminophen could further substantially increase the risk of myocardial infarction and stroke in patients at high cardiovascular risk or, in particular, with established cardiovascular or cerebrovascular disease.[32,33] Importantly, more antihypertensive therapy may have to be prescribed to counter the rise in BP, leading to increased costs.[34]

NSAIDs most likely induce a rise in BP by blocking the synthesis of prostaglandins, which regulate vascular tone and sodium excretion. Acetaminophen is generally considered only a weak inhibitor of prostaglandin synthesis.[35,36] Indeed, and as expected in patients on a background therapy with aspirin,[37] plasma and urinary concentrations of prostacyclin and thromboxane remained unchanged, thus rendering a

Table 2. Laboratory Values Before and After Acetaminophen and Placebo

	Baseline for Treatment Period	Acetaminophen	Baseline for Control Period	Placebo
Hb, g/L	14.5±1.1	14.3±1.0	14.3±1.0	14.3±1.0
Ht, %	41.5±3.0	41.0±2.5	41.0±2.5	41.2±2.8
Sodium, mmol/L	140.4±2.2	140.6±1.9	140.8±1.8	140.4±2.3
Potassium, mmol/L	4.0±0.4	4.0±0.4	4.0±0.3	3.9±0.3
Creatinine, μmol/L	86.9±11.3	86.4±13.9	87.2±13.3	87.9±13.2
Glucose, mmol/L	5.7±1.0	5.6±1.0	5.8±1.3	5.7±1.1
TC, mmol/L	4.3±0.8	4.5±0.9	4.3±0.8	4.4±1.0
HDL-C, mmol/L	1.4±0.4	1.3±0.4	1.3±0.4	1.3±0.4
LDL-C, mmol/L	2.3±0.6	2.4±0.8	2.4±0.7	2.5±0.8
TG, mmol/L	1.4±0.7	1.7±0.9	1.3±0.6	1.3±0.6
ALT, U/L	29.9±8.04	35.1±12.4	28.8±17.0	31.3±10.6
AST, U/L	34.1±16.3	44.8±25.8	35.5±16.6	36.3±21
GGT, U/L	32.9±16.7	54.7±69.9*	37.2±23.2	33.5±17.4
Plasma PGE_2, ng/mL	45.1±18.2	45.3±18.2	47.1±19.8	45.6±21.5
Urinary PGE_2, ng/24 h	404.2±418.1	396.9±358.7	396.4±292.8	395.0±361.5
Plasma $TBXB_2$, ng/mL	34.2±21.4	32.1±24.3	33.2±23.9	34.1±23.9
hs-CRP, mg/L	1.5±1.8	1.5±1.5	1.4±1.3	3.6±6.1
Plasma 8-isoprostanes, pg/mL	1.6±0.9	1.6±0.6	1.5±0.7	1.7±1.1
PRA, $ng \cdot mL^{-1} \cdot /h^{-1}$	3.24±5.03	3.41±5.50	3.43±5.28	3.43±4.69
Aldosterone, pg/mL	72.5±28.7	69.3±23.8	67.5±24.1	74.2±24.8
Urinary sodium, mmol/L	108.0±43.4	105.1±38.8	116.8±39.4	103.5±40.8
Platelet adhesion, %	3.1±1.5	3.9±2.5	3.4±1.6	4.3±1.5

Hb indicates hemoglobin; Ht, hematocrit; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, γ-glutamyltransferase; hs-CRP, high-sensitivity C-reactive protein; PGE_2, prostaglandin E_2; $TBXB_2$, thromboxane B_2; and PRA, plasma renin activity. Data are shown as mean±SD.

*Statistically significant difference ($P<0.05$), acetaminophen versus placebo.

potential COX-2–inhibiting effect unlikely to fully explain the hypertensive effects of acetaminophen under the conditions of the present study.

Although the relative extent of COX-1 versus COX-2 inhibition has potential implications in determining drug safety in patients treated with NSAIDs,[38] concomitant COX-1 inhibition (and reduced thromboxane generation) with aspirin could have counterbalanced any potential COX-2–induced attenuation of prostacyclin release. However, in evaluations of drug safety, theoretical differences cannot serve as a substitute for well-designed randomized trials testing appropriate clinical outcomes. Furthermore, renal function, plasma renin activity, and plasma aldosterone remained unchanged and thus cannot account for the hypertensive effects of acetaminophen, particularly because the majority of patients were treated with angiotensin-converting enzyme inhibitors, angiotensin receptor antagonists, and β- adrenergic blockers.

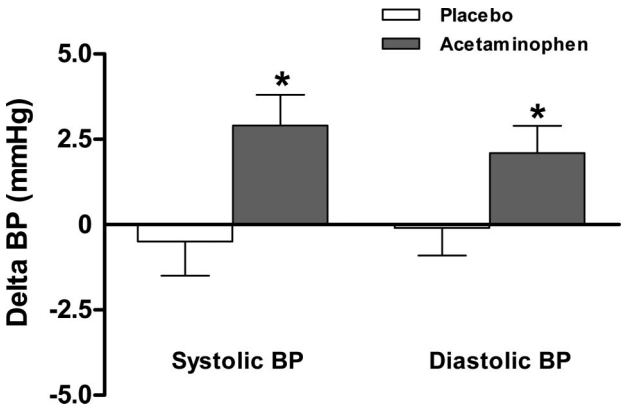

Figure 2. Difference in mean 24-hour ambulatory blood pressure (Delta BP, mm Hg) between baseline and treatment with acetaminophen (grey bars) and placebo (open bars). Data are presented as mean±SEM. Asterisks indicate a statistically significant difference ($P<0.05$) acetaminophen versus placebo.

Unexpectedly, the BP increase induced by acetaminophen was paralleled by a slight increase in rather than the expected baroreceptor-mediated decrease in heart rate. Even though this increase as such was not significant, it suggests a potential central effect of acetaminophen. A predominantly central mechanism of action involving central COX-2 inhibition or a COX variant has been proposed.[39,40] Of interest, a splice variant of COX-1 called COX-3, which is selectively inhibited by acetaminophen and is present mainly in the brain and spinal cord, has been reported.[41] The hypertensive effect of acetaminophen noted in the present study could be mediated by such central COX-3 activity or COX-2 inhibition by acetaminophen[42] or by an indirect activation of cannabinoid CB(1) receptors.[43]

In contrast to the observed effects on BP, the use of acetaminophen showed only a trend toward worsening of endothelial function, an important surrogate marker for vascular homeostasis. It is of note that any potential impairment of endothelial function after treatment with acetaminophen may be explained by a direct effect on the endothelium or secondary via the increase in BP. However, if endothelial function were affected by an increase in BP, 2 weeks of therapy would probably be too short to affect endothelial function. Moreover, a deleterious effect of acetaminophen could have been counterbalanced and masked by the concomitant angiotensin-converting enzyme inhibitors and statin therapy, all of which are known to beneficially affect EPCs and vascular function.[12,44] In contrast to acetaminophen, we demonstrated that celecoxib is able to improve endothelial function and to reduce low-grade chronic inflammation and oxidative stress in patients with CAD.[45]

Some limitations of our study should be taken into account. First, the study is relatively small. This could explain the lack of an effect of acetaminophen on FMD, particularly because the treatment period was short. However, because the patients included in this study did not present with pain and thus could not benefit from the study drug, the number of patients investigated was limited to the minimum required on the basis of sample size calculation. Although the capsules were identical in appearance and taste, a formal test of the adequacy of blinding was not performed. Although there may be a theoretical chance that the patients were able to determine their treatment arm, this appears to be relatively unlikely. Importantly, because of the crossover study design, all patients received both placebo and acetaminophen. Moreover, there was a predominance of men; therefore, the present results may not necessarily be extrapolated to women or to other patients with the exception of those with CAD under optimal pharmacological treatment.

Conclusions

Our study showed that acetaminophen at doses used in daily clinical practice may increase BP in patients with CAD and has no effect on vascular function. Unless the cardiovascular safety of acetaminophen has been cleared in randomized controlled clinical trials specifically addressing the safety of this agent, the use of acetaminophen should be as rigorously evaluated as all traditional antiinflammatory drugs, particularly in patients at increased cardiovascular risk.

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Disclosures

This study was investigator initiated and investigator driven. The authors report no actual or potential conflicts of interest in connection with this study.

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CLINICAL PERSPECTIVE

Nonsteroidal antiinflammatory drugs have been shown to increase the risk for cardiovascular events. In patients with coronary artery disease, current guidelines therefore suggest avoiding such drugs and recommend acetaminophen as the first-line analgesic of choice instead. However, the results of the present prospective study provide the first evidence of a blood pressure elevation in these patients, thus questioning the assumption of the cardiovascular safety of acetaminophen. In view of the established continuous incremental risk of cardiovascular and cerebrovascular disease in relation to blood pressure, an elevation associated with the use of acetaminophen could further increase the risk of myocardial infarction and stroke in patients at high cardiovascular risk or, in particular, in those with established cardiovascular disease. Because the use of acetaminophen is frequent, the blood pressure increase caused by this drug is a potential public health concern. Unless the cardiovascular safety of acetaminophen has been cleared in randomized controlled clinical trials specifically addressing the safety of this agent, the use of acetaminophen should be evaluated as rigorously as all traditional antiinflammatory drugs, particularly in patients at increased cardiovascular risk.

Editorial

Blood Pressure Destabilization on Nonsteroidal Antiinflammatory Agents

Acetaminophen Exposed?

William B. White, MD; Patrick Campbell, MD

It has been conventional wisdom for some time now that nonsteroidal antiinflammatory drugs (NSAIDs), whether selective for inhibition of cyclooxygenase 2 (COX-2) or nonselective, increase blood pressure (BP) or interfere with BP control and that acetaminophen should not have this effect.[1–4] Controlled clinical trials have shown that NSAIDs have heterogeneous effects on clinic and 24-hour BP in normotensive and hypertensive subjects.[3] The inhibition of COX-2 by NSAIDs results in decreased actions of both vasodilatory and natriuretic prostaglandins.[3] In most individuals, homeostasis of plasma volume is reestablished by small, nearly undetectable increases in BP,[5] whereas in patients with impaired excretory function, more substantial volume retention occurs that may be associated with hypertension, edema, and congestive heart failure.[3,5]

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Before 2002, little was known about the effects of NSAIDs on 24-hour BP in patients with arthritis who also had hypertension and/or vascular diseases.[6–8] Because ambulatory BP has improved reproducibility compared with clinic measurements, detection of small but clinically meaningful differences in drug treatment groups[9,10] is more likely to occur. Ambulatory monitoring also allows improved evaluation of pharmacodynamic effects of any drug, including the NSAIDs.[6,7] For example, in the Celecoxib Rofecoxib Efficacy and Safety in Comorbidities Evaluation Trial (CRESCENT), destabilization of systolic BP control occurred for ≈18 of the 24 hours after dosing of rofecoxib at standard osteoarthritis doses of 25 mg each morning.[8] In contrast, no changes from baseline in 24-hour systolic BP were observed with celecoxib or naproxen at their respective standard dosing regimens for osteoarthritis. Of the NSAIDs studied with 24-hour BP monitoring and widely used in clinical practice, ibuprofen, indomethacin, and etoricoxib appear to cause the largest increases in BP, whereas celecoxib and naproxen seem to induce smaller increases in BP and destabilization of BP control (the Table).

In addition to interfering with BP control, NSAIDs at high doses have been shown to increase cardiovascular event rates in placebo-controlled studies of patients with colonic polyps and after coronary artery bypass surgery.[11–14] Because of concerns for these potentially negative cardiovascular effects of the NSAIDs, acetaminophen has typically been suggested as a safer alternative for initial therapy[2,4] in patients with osteoarthritis and comorbid cardiovascular disorders.

In this issue of *Circulation*, the findings of Sudano and coworkers[15] cast some doubt on the cardiovascular safety of acetaminophen, at least from the perspective of BP. The investigators evaluated the effects of acetaminophen at a standard osteoarthritis dose (1 g TID) on ambulatory BP, a variety of serum biomarkers, and platelet and vascular function in 33 patients with known coronary artery disease using a randomized, double-blind, placebo-controlled crossover design. Even with truncated treatment phases of 2 weeks (The investigators wished to minimize exposure time to acetaminophen because these subjects had no pain indication), acetaminophen induced statistically significant increases in mean 24-hour systolic and diastolic BPs from baseline compared with placebo (≈3/2 mm Hg). This increase in 24-hour mean BP is not dissimilar to changes observed with many of the NSAIDs (the Table). Additionally, a small but significant increase in 24-hour heart rate (2 bpm) occurred on acetaminophen relative to placebo.

A comprehensive attempt by the investigators to obtain mechanistic data associated with the effect of acetaminophen on BP was inconclusive. Small relative reductions from baseline in brachial artery flow-mediated dilation were noted in the acetaminophen arm (−5% compared with placebo) but were not statistically different between acetaminophen and placebo, nor was there a significant difference in endothelial-independent flow-mediated dilation. In addition, the investigators found no effects of acetaminophen on platelet adhesion, the proportion of endothelial progenitor cells, concentrations of highly sensitive C-reactive protein, plasma, or urinary concentrations of prostaglandin E_2 or thromboxane B_2. Safety serum chemistries showed a statistically significant increase in the hepatic enzyme γ-glutamyltransferase on acetaminophen treatment compared with placebo.

What Do We Know About the Mechanism of Acetaminophen That Could Lead to a BP-Destabilizing Effect?

Although one of the most widely used analgesics worldwide, the mode of action for relieving pain by acetaminophen has

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Table. Effects of Various NSAIDs on Ambulatory BP

Study	Design and Trial Duration	Patient Population	n	Age, y	Study Drugs	Baseline 24-H BP, mm Hg	Change in 24-h BP, mm Hg
Izhar et al[7]	Randomized, crossover, active controlled, 8 wk	Hypertensive	25	58	Celecoxib 200 mg QD	129/80	1.6/1.9
		Osteoarthritis		58	Diclofenac 75 mg BID	129/79	4.2*/3.0*
MacDonald et al[24]	Parallel, double-blind, active controlled, 4 wk	Osteoarthritis	787	65	Lumiracoxib 100 mg QD	127/74	−2.7/−1.5
		Hypertensive		64	Ibuprofen 600 mg TID	127/74	2.2*/0.5*
Morgan et al[25]	Parallel, randomized, double-blind, crossover, 6 wk	Hypertensives Nonarthritis	41	69	Amlodipine+indomethacin 50 mg BID	141/77	1.0/0.0
				72	Enalapril+indomethacin 50 mg BID	134/73	12.0*/5.0*
Polonia et al[26]	Randomized, crossover, single-blind, 1 wk of NSAID	Hypertensives Nonarthritis	18	53	Nifedipine+indomethacin 75 mg	135/88	0.3/0.6
				53	Enalapril+indomethacin 75 mg	135/87	6.8*/4.6*
Schwartz et al[27]	Parallel, double-blind, placebo-, and active-controlled, 15 d	Elderly normal Controlled diet	85	66	Etoricoxib 90 mg QD	NR	7.7*/3.2*
				65	Celecoxib 200 mg BID	NR	2.4*/1.1
				67	Naproxen 500 mg BID	NR	3.6*/1.4*
				66	Placebo	NR	−2.4/−0.8
Sowers et al[8]	Parallel, double-blind, active-controlled, 6 and 12 wk	Osteoarthritis Hypertension	404	64	Rofecoxib 25 mg QD	132/76	4.2*/1.5*
				62	Celecoxib 200 mg QD	132/76	−0.1/−0.1
	Type 2 diabetes mellitus			64	Naproxen 500 mg BID	134/76	−0.8/−1.0
Sudano et al[15]	Randomized, double-blind crossover, placebo-controlled, 2 wk	Coronary artery disease	33	61	Acetaminophen 1 g TID	122/73	2.9*/2.2*
				61	Placebo	123/74	−0.5/0.2
White et al[6]	Parallel, double-blind, placebo-controlled, 4 wk	Hypertensive On ACE inhibitor	178	55	Celecoxib 200 mg BID	135/84	2.6/1.5
				53	Placebo	131/82	1.0/0.3

DM indicates diabetes mellitus; ACE, angiotensin-converting enzyme.
*Statistically greater than comparator.

been poorly understood for nearly a century, but several interesting hypotheses have recently been reported.[16–20] It is questionable whether these novel mechanisms of action that may convey pain relief by acetaminophen could theoretically translate to a pressor effect in susceptible individuals. Acetaminophen is an indirect COX-2 selective inhibitor that acts via a peroxidase site on prostaglandin H_2 synthetase 2 and reduces the conversion of arachidonic acid to prostaglandin H_2.[16] It is not known whether this directly affects vascular resistance and BP. Another carefully described mechanism of action for analgesic benefits of acetaminophen is the indirect activation of the cannabinoid receptors. *N*-arachidonoyl phenylamine, a metabolite of acetaminophen, has been shown to indirectly stimulate endogenous cannabinoid release.[17,18] However, stimulation of cannabinoid release seems to lower BP modestly, not increase it.[19] Finally, acetaminophen and other NSAIDs have been shown to inhibit *N*-methyl-D-aspartic acid receptors, which play a role in pain neurotransmission[20] and in vasodilation.[21] When stimulated, *N*-methyl-D-aspartic acid receptors release nitric oxide as a neurotransmitter in the spinal cord. The release of nitric oxide may modulate arachidonic acid metabolism by altering cyclooxygenase activity.[21]

Where Does Acetaminophen Fit in the Management of Arthritis and Pain in Patients With Cardiovascular Disease?

The data reported by Sudano et al imply that development of asymptomatic hypertension or destabilization of treated, controlled hypertension could occur in some patients with heart or vascular disease when treated with standard long-term doses of acetaminophen. However, the interpretation of most other findings of the study, with the exception of platelet adhesion, is limited by its brevity (only 2 weeks of exposure to acetaminophen); results for the other biomarkers and functional assessments studied cannot be considered conclusive. Additionally, although the study did demonstrate a significant increase in BP after only 2 weeks of therapy, it is possible that longer-term administration of acetaminophen could induce more substantial increases in BP than was observed here. In the future, it will be important to explore the effects of acetaminophen in a broader population that might include patients with higher levels of BP, arthritis and/or chronic pain, and mild to moderate renal disease and those on various antihypertensive drug classes. The narrow patient population studied limits our ability to apply these results to the general population.

It is not likely that the clinical status of acetaminophen will be effectively changed in the short term by the results of this new study. However, clinical cardiologists should be aware that although acetaminophen is relatively effective for some forms of minor pain, it is quite ineffective for inflammatory diseases such as moderate to advanced osteoarthritis or rheumatoid arthritis.[1] In most clinical trials of these latter patient populations, it has not been proven to be superior to placebo. In addition, the hepatic safety of acetaminophen, particularly in doses >3 g/d, has been under great scrutiny

recently because the drug is implicated as one of the most common causes for liver transplantation in the United States.[22]

In conclusion, despite broad recommendations to use acetaminophen as first-line therapy for pain and arthritis in patients with heart and vascular disease,[2,23] the agent is simply not that effective, and as supported by new findings by Sudano et al, a lot more is unknown about this drug from a cardiovascular safety perspective than we know about the conventional NSAIDs and selective COX-2 inhibitors.[3,4]

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KEY WORDS: Editorials ■ acetaminophen ■ ambulatory blood pressure monitoring ■ clinical trials ■ coronary artery disease ■ hypertension ■ nonsteroidal antiinflammatory drugs

Non-Narcotic Analgesic Dose and Risk of Incident Hypertension in US Women

John P. Forman, Meir J. Stampfer, Gary C. Curhan

Abstract—Acetaminophen, ibuprofen, and aspirin are the most commonly used drugs in the United States. Although the frequency of their use has been associated with hypertension, prospective data examining the dose of these drugs and risk of hypertension are lacking. Furthermore, whether certain indications for analgesic use, particularly headache, mediate the association is unclear. We conducted 2 prospective cohort studies among older women 51 to 77 years of age (n=1903) from the Nurses' Health Study I and younger women 34 to 53 years of age (n=3220) from the Nurses' Health Study II who completed detailed supplemental questionnaires pertaining to their analgesic use and who did not have hypertension at baseline. We analyzed incident hypertension according to categories of average daily dose of acetaminophen, nonsteroidal anti-inflammatory drugs, and aspirin. Information on indications for analgesic use as well as relevant confounders was also gathered prospectively. Compared with women who did not use acetaminophen, the multivariable adjusted relative risk for those who took >500 mg per day was 1.93 (1.30 to 2.88) among older women and 1.99 (1.39 to 2.85) among younger women. For nonsteroidal anti-inflammatory drugs, similar comparisons yielded multivariable relative risks of 1.78 (1.21 to 2.61) among older women and 1.60 (1.10 to 2.32) among younger women. These associations remained significant among women who did not report headache. Aspirin dose was not significantly associated with hypertension. Higher daily doses of acetaminophen and nonsteroidal anti-inflammatory drugs independently increase the risk of hypertension in women. Because acetaminophen and nonsteroidal anti-inflammatory drugs are commonly used, they may contribute to the high prevalence of hypertension in the United States. **(*Hypertension*. 2005;46:500-507.)**

Key Words: epidemiology ■ lifestyle ■ risk factors ■ human ■ women

Acetaminophen, ibuprofen, and aspirin are the 3 most frequently used drugs in the United States.[1] These drugs may lead to high blood pressure through various mechanisms, including inhibition of vasodilatory prostaglandins.[2–5] In addition, nonsteroidal anti-inflammatory drugs (NSAIDs) increase renal sodium reabsorption,[6–8] and acetaminophen and NSAIDs may impair endothelial function.[9–17]

In 2 large prospective cohorts of women, we previously reported an association between the frequency of analgesic use (days per month) and the risk of developing hypertension.[18,19] The major criticisms of these previous analyses were the lack of information on drug doses used by participants and the indications for their use, in particular, the concern that headache as a result of higher blood pressure may lead to analgesic use (confounding by indication).

To address these concerns and to further examine this important public health issue, we studied the association between dose of nonnarcotic analgesic drug use, indication for use, and the risk of incident hypertension among subcohorts consisting of 1903 older female participants of Nurses' Health Study I (NHS I) and 3220 younger female participants of NHS II without a history of hypertension at baseline.

Methods

Nurses' Health Studies

The NHS I cohort was assembled in 1976, when 121 700 female nurses 30 to 55 years of age returned a mailed questionnaire. Subsequent questionnaires have been mailed every 2 years to update information on health-related behaviors and medical events. On the 1990, 1992, and 1998 questionnaires, we inquired about the frequency of use of acetaminophen, NSAIDs, and aspirin.

NHS II is an independent cohort of 116 671 female registered nurses who were 25 to 42 years of age when they returned an initial questionnaire in 1989. These women are also followed with similar biennial questionnaires. Beginning in 1995, we inquired about the frequency of use of nonnarcotic analgesics.

Study Populations

For this study, subcohorts were assembled within the older cohort (NHS I) and within the younger cohort (NHS II). The assembly of these subcohorts and the delineation of the populations for the analysis of incident hypertension is detailed in the Figure. These subcohorts were originally assembled to obtain detailed information on analgesic use and study associations between analgesics and renal function.[20] None of the participants of these analyses were cases from the previously published studies that examined frequency of analgesic use and hypertension in NHS I[18] and NHS II.[19] The

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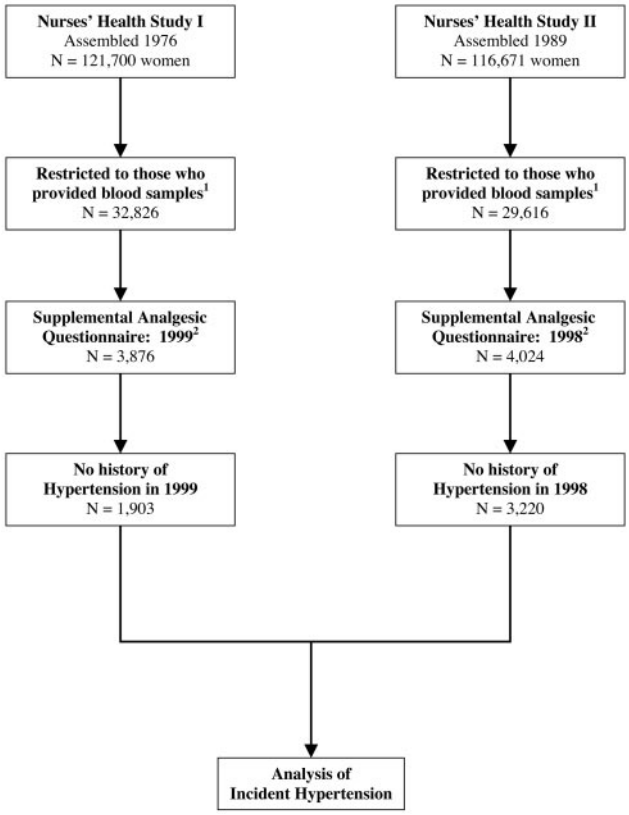

Assembly of the subcohorts for analysis of incident hypertension. 1. The purpose of restricting the study population to those who had blood samples available was to examine the association between analgesic use and renal function.[20] 2. To enrich the subcohorts with participants likely to have either high or low analgesic intake, recipients of the supplemental analgesic questionnaires reported using either no analgesics or a high frequency of analgesics (≥15 days per month) on the main biennial questionnaires that are sent to all participants of NHS I and NHS II. The supplemental questionnaire was sent to 4238 women in NHS I and 4454 women in NHS II. The figure shows the numbers of women who responded to the supplemental questionnaires (91% and 90%, respectively). Participants in these subcohorts also received the main biennial questionnaire that is sent to all participants of NHS I and NHS II.

institutional review board at Brigham and Women's Hospital reviewed and approved this study, including that participants provided implied consent by virtue of returning their questionnaires.

Assessment of Analgesic Use and Indications

Each supplementary questionnaire collected detailed information specifically about the participant's current use of acetaminophen, NSAIDs, and aspirin, including frequency of current use (in days per month), number of tablets per day when used, dosage per tablet, brand used, and the indications for use. From this information, we first calculated an estimated average monthly dose of each analgesic class by multiplying together the days/month, tablets/day, and dose/tablet; we then computed the average daily dose by dividing by 30 days/month. We classified participants into 1 of 4 categories of current use for each analgesic: acetaminophen (0 mg per day, 1 to 100 mg per day, 101 to 500 mg per day, and >500 mg per day); aspirin (0 mg per day, 1 to 100 mg per day, 101 to 400 mg per day, and >400 mg per day); and NSAIDs (0 mg per day, 1 to 100 mg per day, 101 to 400 mg per day, and >400 mg per day). Because ibuprofen was by far the most commonly used NSAID (accounting for 67% of NSAID users in NHS I and 80% of NSAID users in NHS II), the doses of nonibuprofen NSAIDs were converted into roughly equivalent doses of ibuprofen using the following scheme: naproxen, 2-fold higher potency per mg; celecoxib, 4-fold higher potency per mg; other NSAIDs including ketoprofen, diclofenac, indomethacin, and others, 10-fold higher potency per mg.[21] The combination of ibuprofen and naproxen accounted for 81% of NSAIDs used in NHS I and 92% of NSAIDs used in NHS II. When information regarding type of NSAID used was missing (3% in NHS I and 2% in NHS II), ibuprofen was assumed.

The supplementary questionnaires also asked participants to report the indication for use of each class of analgesic. For acetaminophen and NSAIDs, possible response categories were "headache," "backache," "muscle or joint pain," "menstrual cramps," and "other." For aspirin, "prevent heart disease" was added to these categories. Participants were allowed to report >1 indication. Our analysis examined the potential role of headache as an indication for use.

Assessment of Hypertension

Hypertension was self-reported in these cohorts of health professionals on biennial questionnaires, and self-reported hypertension has been shown to be highly reliable. In a subset of women who reported hypertension, medical record review confirmed a documented blood pressure >140/90 in 100%; additionally, self-reported hypertension was predictive of subsequent cardiovascular events.[22]

Women were considered to have prevalent hypertension at the time they returned the first supplementary questionnaire if they reported a diagnosis of hypertension on any previous main biennial questionnaire (sent to all NHS I and NHS II members) or reported hypertension on the supplementary questionnaire (which only members of these subcohorts received). For the analysis of incident hypertension, women with prevalent hypertension were excluded. In those without prevalent hypertension at baseline, women were considered to have incident hypertension if they reported an initial diagnosis of hypertension after the return of the supplementary questionnaire.

Assessment of Other Factors

Age, body mass index (BMI; kg/m^2), smoking status, physical activity (metabolic equivalent task scores), and oral contraceptive use (in NHS II) were ascertained from the main biennial questionnaires returned just before the supplemental analgesic questionnaire. Intakes of alcohol, caffeine, folate, sodium, potassium, magnesium, and calcium were ascertained from semiquantitative food frequency questionnaires that were mailed to participants of NHS I and II every 4 years. The food frequency questionnaire returned just before the analgesic supplementary questionnaire was used to obtain this information. Information on family history of hypertension was available on the 1992 (NHS I) and 1989 (NHS II) questionnaires. We obtained self-reported blood pressure from the supplementary questionnaire. Systolic blood pressure was reported in 9 categories (<105, 105 to 114, 115 to 124, 125 to 134, 135 to 144, 145 to 154, 155 to 164, 165 to 174, and ≥175 mm Hg), and diastolic blood pressure was reported in 7 categories (<65, 65 to 74, 75 to 84, 85 to 89, 90 to 94, 95 to 104, and ≥105 mm Hg). A participant's blood pressure was defined as the middle systolic and middle diastolic value of the reported category. Clinician visits (during which blood pressure measurement is likely to occur) were reported in 2000 (NHS I) and 2001 (NHS II).

Statistical Analysis

For each participant, person months of follow-up were counted from the date of return of the supplementary questionnaire to the date of return of the last biennial questionnaire and allocated according to exposure status. Incidence rates were computed by dividing the number of new cases of hypertension by the number of person years in the particular category of analgesic use. The association between the previously defined categories of analgesic use and incident hypertension were analyzed using Cox proportional hazards regression. We computed hazard ratios (reported as relative risks [RRs]) for age-adjusted models, as well as multivariable-adjusted models that included age (continuous), BMI (continuous), physical activity

(quintiles), smoking (never, past, current), family history of hypertension (yes/no), and intakes of alcohol, caffeine, and other nutrients (quintiles). We also included oral contraceptive use (yes/no) in multivariable models when examining the younger NHS II cohort. In all models, we simultaneously adjusted for each of the 3 classes of analgesics. In each class of analgesic, the reference category consisted of those with no use of that class. Age-adjusted and multivariable tests for linear trend were assessed using the median daily analgesic dose within each exposure category.

Because it has been suggested that the presence of headache may be the focus of an indirect link between analgesic use and hypertension,[23] we performed secondary analyses restricting the study populations to those women who did not report headache as an indication for analgesic use. To reduce ascertainment bias, we performed other secondary analyses limited to women who reported having ≥1 clinician examination during follow-up.

For all RRs, we calculated 95% confidence intervals (CIs). All *P* values are 2-tailed. Statistical tests were performed using SAS statistical software, version 9 (SAS Institute Inc).

Results

Participant Characteristics

The baseline characteristics of those included in the primary analysis, according to categories of average daily analgesic dose, are given in Table 1. Among the older cohort (NHS I; Table 1A), individuals who did not take analgesics had lower BMI and lower systolic and diastolic blood pressure, whereas physical activity was higher among nonusers of acetaminophen. In the younger cohort (NHS II; Table 1B), systolic and diastolic blood pressures were lower in those who did not use analgesics, whereas BMI was lower among nonusers of acetaminophen and NSAIDs.

During 5268 person years of follow-up in NHS I, we identified 211 incident cases of hypertension. During 13 405 person years of follow-up in NHS II, we identified 299 incident cases of hypertension.

Incident Hypertension

Nurses' Health Study I

In the older women, a higher average daily dose of acetaminophen and NSAIDs was associated with an increased risk of incident hypertension (Table 2A). Older women whose daily dose of acetaminophen exceeded 500 mg had a 93% increased risk of developing hypertension after controlling for potential confounders compared with acetaminophen nonusers (multivariable RR, 1.93; 95% CI, 1.30 to 2.88; *P* trend <0.001). Compared with nonusers of NSAIDs, those who consumed >400 mg per day of NSAIDs had a 78% increased risk of hypertension (multivariable RR, 1.78; 95% CI, 1.21 to 2.61; *P* trend=0.01). We also examined whether NSAID doses exceeding 800 mg per day conferred even higher risk by splitting the highest category of NSAID dose into 401 to 800 mg per day and >800 mg per day groups; compared with those who did not use NSAIDs, women whose usual dose was >800 mg per day had a 2.2-fold higher risk of incident hypertension compared with nonusers (multivariable RR, 2.17; 95% CI, 1.38 to 3.42). Aspirin dose was not associated with incident hypertension.

Because women who take analgesics may be more likely to visit their clinicians (and thus more likely to be diagnosed with hypertension), we analyzed the subset of women (n=1804 with 204 cases) who reported ≥1 examination during the period of follow-up, in which blood pressure was likely to be measured. The RR comparing the highest to lowest category of use remained significantly elevated for acetaminophen (RR, 1.96; 95% CI, 1.30 to 2.96) and NSAIDs (RR, 1.66; 95% CI, 1.12 to 2.46). After adjusting for baseline systolic and diastolic blood pressure, acetaminophen (RR, 1.68; 95% CI, 1.11 to 2.56; *P* trend=0.009) and NSAIDs (RR, 1.74; 95% CI, 1.16 to 2.61; *P* trend=0.02) remained associated with incident hypertension. Further adjustment for sodium, potassium, magnesium, and calcium did not materially alter the results.

Nurses' Health Study II

Among the younger women, a higher average daily dose of acetaminophen and NSAIDs was also associated with an increased risk of incident hypertension (Table 2B). Younger women whose average daily acetaminophen intake was >500 mg had a 2-fold higher risk of developing hypertension compared with those who did not use acetaminophen (multivariable RR, 1.99; 95% CI, 1.39 to 2.85; *P* trend <0.001). Compared with nonusers of NSAIDs, women whose intake exceeded 400 mg per day had a 60% increased risk of hypertension (multivariable RR, 1.60; 95% CI, 1.10 to 2.32; *P* trend=0.04). The risk among women whose usual NSAID dose exceeded 800 mg per day was similar (multivariable RR, 1.61; 95% CI, 1.06 to 2.44). Aspirin dose was marginally associated with an increased risk of incident hypertension in younger women (*P* trend=0.06).

In younger women who reported ≥1 examination during the follow-up (n=3030; 289 cases), results for acetaminophen (RR, 1.96; 95% CI, 1.36 to 2.85) and NSAIDs (RR, 1.58; 95% CI, 1.09 to 2.30) were not materially different from the entire sample. After additionally controlling for baseline blood pressure, acetaminophen remained significantly associated with hypertension (RR, 1.64; 95% CI, 1.10 to 2.45; *P* trend=0.02), but the association between NSAIDs and hypertension was no longer significant (RR, 1.45; 95% CI, 0.97 to 2.16; *P* trend=0.21). Controlling for intake of sodium, potassium, magnesium, and calcium did not substantially change the results.

Analgesic Use and Incident Hypertension in Those Without Headache

To address the possibility that the association between analgesic use and hypertension may be mediated by headache, we repeated our analyses among women without headache. Among women who did not report headache as an indication for analgesic use (n=1239 with 123 cases in NHS I; n=822 with 82 cases in NHS II), intakes of acetaminophen and NSAIDs were associated with incident hypertension in the older and younger cohorts (Table 3). Compared with nonusers of acetaminophen, older women who consumed >500 mg per day had a 2.4-fold increased risk of hypertension; in younger women, the same comparison yielded a 4.7-fold increased risk. Among the older women without headache, those whose NSAID consumption exceeded 400 mg per day had a 1.75-fold higher risk of incident hypertension compared with NSAID nonusers; in younger women, the same compar-

TABLE 1. A. Baseline Characteristics of NHS I Participants According to Category of Analgesic Use

	Category of Acetaminophen Use (mg/day)			
	0	1–100	101–500	>500
No. of participants	1202	200	234	267
Age, years	64.0	63.9	63.6	64.0
BMI, kg/m^2	24.7	25.1	25.6	26.3
Smoking history, %				
Past	41.8	48.5	43.2	53.2
Current	9.3	6.0	4.7	10.1
Physical activity, METs/week	22.5	20.9	19.4	16.8
Family history of HTN, %	38.4	39.5	44.4	37.1
Alcohol intake, g/day	5.6	5.1	5.3	4.5
Caffeine intake, mg/day	191	209	205	189
Folate intake, μg/day	633	660	712	669
Baseline SBP (mm Hg)	124	124	126	126
Baseline DBP (mm Hg)	75	75	76	76
	Category of NSAID Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	1146	223	155	379
Age, years	64.6	62.9	62.3	63.2
BMI, kg/m^2	24.6	24.8	25.6	26.6
Smoking history, %				
Past	42.2	48.0	45.2	48.2
Current	9.2	7.6	7.1	7.6
Physical activity, METs/week	21.8	23.7	17.1	19.4
Family history of HTN, %	37.7	45.7	36.8	40.4
Alcohol intake, g/day	5.1	5.6	5.1	6.0
Caffeine intake, mg/day	184	200	225	210
Folate intake, μg/day	648	634	683	654
Baseline SBP (mm Hg)	124	124	125	126
Baseline DBP (mm Hg)	75	75	75	76
	Category of Aspirin Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	1122	304	292	185
Age, years	63.9	64.3	64.2	63.5
BMI, kg/m^2	24.8	25.5	25.6	25.5
Smoking history, %				
Past	42.8	47.0	46.9	44.9
Current	8.9	4.9	6.5	15.1
Physical activity, METs/week	21.5	19.1	23.5	18.6
Family history of HTN, %	38.7	43.8	36.0	38.9
Alcohol intake, g/day	5.2	5.3	5.7	5.6
Caffeine intake, mg/day	185	195	219	215
Folate intake, μg/day	627	686	684	682
Baseline SBP (mm Hg)	123	126	126	124
Baseline DBP (mm Hg)	75	75	76	75

METs indicates metabolic equivalent task scores; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 1. B. Baseline Characteristics of NHS II Participants According to Category of Analgesic Use

	Category of Acetaminophen Use (mg/day)			
	0	1–100	101–500	>500
No. of participants	1437	606	845	332
Age, years	45.4	44.9	45.0	45.5
BMI, kg/m^2	25.7	25.8	26.1	27.3
Smoking history, %				
Past	27.7	25.4	28.6	28.0
Current	7.7	7.2	7.5	8.0
Oral contraceptive use, %	3.1	4.7	3.1	3.5
Physical activity, METs/week	20.2	18.9	18.5	17.5
Family history of HTN, %	51.1	45.2	48.4	52.9
Alcohol intake, g/day	4.8	4.2	4.4	2.8
Caffeine intake, mg/day	238	223	252	236
Folate intake, μg/day	651	647	634	637
Baseline SBP (mm Hg)	116	116	117	119
Baseline DBP (mm Hg)	72	72	73	74
	Category of NSAID Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	756	790	708	966
Age, years	45.6	44.7	45.0	45.4
BMI, kg/m^2	25.0	24.8	26.3	27.4
Smoking history, %				
Past	24.4	24.9	30.6	30.0
Current	8.2	6.6	7.2	8.2
Oral contraceptive use, %	3.3	4.0	4.4	2.4
Physical activity, METs/week	20.7	19.2	18.1	19.0
Family history of HTN, %	47.0	47.6	52.4	50.8
Alcohol intake, g/day	3.8	4.3	4.3	5.0
Caffeine intake, mg/day	229	224	242	255
Folate intake, μg/day	647	650	617	657
Baseline SBP (mm Hg)	115	115	117	118
Baseline DBP (mm Hg)	71	72	73	73
	Category of Aspirin Use (mg/day)			
	0	1–100	101–400	>400
No. of participants	1996	559	451	214
Age, years	44.7	45.8	46.0	46.3
BMI, kg/m^2	26.0	26.0	25.8	26.4
Smoking history, %				
Past	25.9	29.8	30.2	31.2
Current	6.2	7.1	9.8	17.3
Oral contraceptive use, %	3.9	2.4	2.8	3.0
Physical activity, METs/week	18.8	18.9	23.4	15.6
Family history of HTN, %	49.2	48.0	50.5	54.0
Alcohol intake, g/day	4.2	4.8	5.0	4.0
Caffeine intake, mg/day	230	259	247	248
Folate intake, μg/day	628	680	677	629
Baseline SBP (mm Hg)	116	117	117	118
Baseline DBP (mm Hg)	72	72	73	73

METs indicates metabolic equivalent task scores; HTN, hypertension; SBP, systolic blood pressure; DBP, diastolic blood pressure.

TABLE 2. Average Daily Dose of Non-Narcotic Analgesics and the Risk of Incident Hypertension

A. NHS I

	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* trend
Person years	3365	551	636	716	
Cases	107	20	34	50	
Age-adjusted RR (95% CI)	1.0 (reference)	0.78 (0.47, 1.31)	1.42 (0.92, 2.20)	2.02 (1.38, 2.97)	<0.001
Multivariable* RR (95% CI)	1.0 (reference)	0.82 (0.48, 1.39)	1.33 (0.84, 2.08)	1.93 (1.30, 2.88)	<0.001
NSAIDs	0	1–100	101–400	> 400	*P* trend
Person years	3212	611	422	1024	
Cases	99	30	22	60	
Age-adjusted RR (95% CI)	1.0 (reference)	1.74 (1.09, 2.76)	1.48 (0.86, 2.51)	1.89 (1.31, 2.72)	0.003
Multivariable* RR (95% CI)	1.0 (reference)	1.72 (1.07, 2.78)	1.53 (0.89, 2.66)	1.78 (1.21, 2.61)	0.01
Aspirin	0	1–100	101–400	>400	*P* trend
Person years	3127	827	808	506	
Cases	108	43	37	23	
Age-adjusted RR (95% CI)	1.0 (reference)	1.34 (0.91, 1.99)	1.11 (0.73, 1.70)	1.13 (0.68, 1.86)	0.71
Multivariable* RR (95% CI)	1.0 (reference)	1.28 (0.86, 1.92)	1.19 (0.77, 1.83)	1.12 (0.67, 1.86)	0.66

B. NHSII

	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* trend
Person years	6066	2531	3495	1313	
Cases	118	47	76	58	
Age-adjusted RR (95% CI)	1.0 (reference)	1.02 (0.72, 1.45)	1.10 (0.81, 1.50)	2.14 (1.53, 2.99)	<0.001
Multivariable† RR (95% CI)	1.0 (reference)	1.11 (0.76, 1.60)	1.09 (0.79, 1.50)	1.99 (1.39, 2.85)	<0.001
NSAIDs	0	1–100	101–400	>400	*P* trend
Person years	3206	3324	2930	3946	
Cases	51	57	74	117	
Age-adjusted RR (95% CI)	1.0 (reference)	1.33 (0.90, 1.98)	1.82 (1.25, 2.65)	2.06 (1.46, 2.91)	<0.001
Multivariable† RR (95% CI)	1.0 (reference)	1.22 (0.80, 1.85)	1.54 (1.04, 2.28)	1.60 (1.10, 2.32)	0.04
Aspirin	0	1–100	101–400	> 400	*P* trend
Person years	8332	2345	1854	874	
Cases	179	46	50	24	
Age-adjusted RR (95% CI)	1.0 (reference)	0.88 (0.62, 1.24)	1.36 (0.98, 1.90)	1.26 (0.80, 1.98)	0.09
Multivariable† RR (95% CI)	1.0 (reference)	0.89 (0.62, 1.27)	1.38 (0.96, 1.97)	1.35 (0.84, 2.18)	0.06

All models simultaneously adjust for intake of all 3 analgesics classes.

*Adjusted for age, BMI, physical activity, smoking, alcohol, caffeine, family history, and intake of folate; †adjusted for age, BMI, physical activity, oral contraceptive use, smoking, alcohol, caffeine, family history, and intake of folate.

ison yielded a 3.7-fold increased risk. Aspirin dose remained unassociated with risk of hypertension.

Discussion

We observed that NSAIDs as well as a higher average daily dose of acetaminophen were significantly and independently associated with a higher risk of incident hypertension. In those without headache, acetaminophen and NSAIDs remained independently associated with hypertension. Aspirin dose was not significantly associated with hypertension. We are unaware of other prospective studies that have examined a dose response between analgesic use and incident hypertension or addressed the possibility of headache as a mediator of the association between analgesic use and hypertension.

These results confirm and expand on our previous reports that frequency of acetaminophen and NSAID use increases the risk of incident hypertension in women.[18,19] The association between acetaminophen and hypertension may in part be mediated through a potential effect on endothelial function. Endothelial thiols such as glutathione (GSH) may

TABLE 3. Average Daily Dose of Non-Narcotic Analgesics and the Risk of Incident Hypertension Among Those Without Headache as an Indication

A. NHS I					
Among Those Women Without Headache					
	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* Trend
Person years	2593	199	274	389	
Cases	70	7	17	29	
Multivariable* RR (95% CI)	1.0 (reference)	1.03 (0.37, 2.89)	1.42 (0.68, 2.95)	2.38 (1.31, 4.35)	0.005
NSAIDs	0	1–100	101–400	>400	*P* trend
Person years	2322	305	171	656	
Cases	66	11	8	38	
Multivariable* RR (95% CI)	1.0 (reference)	1.99 (0.88, 4.51)	1.35 (0.54, 3.41)	1.75 (1.02, 3.00)	0.06
Aspirin	0	1–100	101–400	>400	*P* trend
Person years	2340	473	407	234	
Cases	77	21	16	9	
Multivariable* RR (95% CI)	1.0 (reference)	0.93 (0.50, 1.73)	1.09 (0.56, 2.11)	0.88 (0.36, 2.16)	0.89
B. NHSII					
Among Those Women Without Headache					
	Average Daily Dose (mg/day)				
Acetaminophen	0	1–100	101–500	>500	*P* trend
Person years	2590	201	374	270	
Cases	48	3	12	19	
Multivariable* RR (95% CI)	1.0 (reference)	0.73 (0.12, 4.43)	0.62 (0.21, 1.80)	4.68 (1.74, 12.6)	0.002
NSAIDs	0	1–100	101–400	>400	*P* trend
Person years	1328	495	519	1094	
Cases	20	10	10	42	
Multivariable* RR (95% CI)	1.0 (reference)	2.16 (0.67, 6.96)	1.01 (0.33, 3.10)	3.67 (1.53, 8.79)	0.002
Aspirin	0	1–100	101–400	>400	*P* trend
Person years	2529	339	377	191	
Cases	57	6	13	6	
Multivariable* RR (95% CI)	1.0 (reference)	0.42 (0.12, 1.40)	1.19 (0.41, 3.49)	1.70 (0.37, 7.70)	0.39

*All models simultaneously adjust for intake of all 3 analgesics classes, as well as age, BMI, physical activity, smoking, alcohol, caffeine, family history of hypertension, and intake of folate. Oral contraceptive use was included in the analysis of NHS II.

mediate some of the beneficial effects of NO.[9,10] Compounds similar to acetaminophen deplete GSH and can cause endothelial dysfunction in animal models, and infusion of GSH in humans enhances endothelial function.[11–14] Also, inhibition of vasodilatory prostaglandins may play a role.[2,4] In addition to the inhibition of vasodilatory prostaglandins[3,5] and increasing renal sodium and water reabsorption,[6–8] NSAIDS may also exert a deleterious effect on endothelial function. For example, indomethecin increases endothelin-1 production.[15,16] Although aspirin also inhibits prostaglandin synthesis,[5] it has not been associated with endothelial dysfunction. On the contrary, aspirin may improve endothelial function, as has been documented in patients with atherosclerosis.[24]

In the 2 previous studies from these cohorts, we found an association between frequency of aspirin use and incident hypertension among the older women and a marginally significant association among the younger women.[18,19] In the present study, we did not detect an association between aspirin dose and hypertension. However, the risk estimates for aspirin are consistent among the studies, and there may have been insufficient power in the subcohorts to detect a modest association.

The relationship between NSAIDs and hypertension has been examined previously in epidemiologic and small interventional studies. Two community-based cross-sectional studies in elderly populations found significant associations between NSAID use (yes or no, rather than dose used) and hypertension, with odds ratios of 1.4 to 2.2, after adjusting for various potential confounders such as age and BMI.[25,26] A large case-control study of elderly Medicaid beneficiaries

reported a 1.6-fold increased odds of filling an initial prescription for antihypertensive medication if an NSAID prescription was filled during the previous 60 days after controlling for age, sex, race, nursing home status, and health care utilization.[27] Two meta-analyses of randomized trials reported that NSAIDs raised mean blood pressure.[28,29] One found that among 771 primarily white participants of various trials, NSAIDs increased mean blood pressure by 5 mm Hg overall (95% CI, 1.2 to 8.7).[28] However, the effect was largely limited to those participants receiving therapy for existing hypertension (5.4 mm Hg increase; 95% CI, 1.2 to 9.6); among the studies of normotensive individuals, blood pressure increases with NSAIDs were small and not statistically significant. Furthermore, in the trials in which antihypertensive medicines were administered, NSAIDs were found to antagonize the effect of these drugs.[28] The second meta-analysis found a 3 mm Hg increase in mean blood pressure with NSAIDs that was also limited to participants with pre-existing hypertension.[29] Additionally, only certain NSAIDs such as indomethecin and naproxen were associated with increased blood pressure, whereas others such as ibuprofen and sulindac were not.[29] Together, these meta-analyses suggest that NSAIDs may antagonize the efficacy of antihypertensive medication.

Less information has been published regarding the potential effect of acetaminophen on blood pressure and risk of hypertension. A short-term randomized crossover study of 20 patients with treated hypertension reported that 1000 mg given 4× per day of acetaminophen versus placebo for 4 weeks led to a statistically significant 4 mm Hg rise in systolic blood pressure.[30] Aspirin has also received less attention. A prospective cohort study of 1040 women found no association between baseline aspirin use (determined by urinary salicylates) and the odds of incident hypertension over a 20-year period.[31] In the 2 meta-analyses of NSAIDs mentioned above, aspirin use was also examined and had no significant effect on blood pressure.[28,29]

Our study has strengths and weaknesses that deserve mention. We determined analgesic use with detailed questionnaires before the diagnosis of hypertension, and we used reliable information on many known hypertension risk factors. In addition, we were able to examine average daily dose as the primary exposure rather than simply examining frequency of use. Finally, the information we gathered on indications for analgesic use allowed us to reanalyze these associations in those without headache. As a potential weakness, we did not directly examine participants during follow-up to confirm self-reported hypertension; however, all participants were registered nurses, and hypertension reporting has been shown previously to be reliable in our cohorts.[22] Also, it was possible that women taking analgesics were more likely to visit their clinicians and thus more likely to be diagnosed with hypertension. However, most women in this study (91% to 95%) had ≥1 clinician visit during follow up, and after limiting our analysis to this subset, the results were unchanged. Random misclassification of analgesic use may have occurred because of inaccuracy of reporting, but in this prospective study, such misclassification, if anything, would have led to an underestimation of the true association. Residual confounding is always a potential concern in observational studies, but we carefully adjusted for factors such as BMI, physical activity, and other known hypertension risk factors in our multivariable models; such adjustment had only a modest impact on the associations, and we are unaware of common medical conditions that are simultaneously indications for analgesic use and independently associated with hypertension. Finally, we had insufficient power to dissect the relationships between individual NSAID types, such as ibuprofen versus naproxen, and the risk of hypertension. However, ibuprofen was by far the most commonly used (67% to 80%) in this data set, as it is nationwide.[1]

Perspectives

Although clinicians may believe that NSAIDs have the potential for untoward renal and hemodynamic consequences, it is commonly held that acetaminophen is safe. These data add further support to the hypothesis that acetaminophen and NSAIDs may independently elevate the risk of hypertension. Given their common consumption and the high prevalence of hypertension, our results have substantial public health implications, and suggest that these agents be used with greater caution. The contribution of non-narcotic analgesics to the hypertension disease burden merits further study.

Acknowledgments

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Nonsteroidal Antiinflammatory Drugs, Acetaminophen, and the Risk of Cardiovascular Events

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Background—Although randomized trials of cyclooxygenase-2 (COX-2) inhibitors have shown increased cardiovascular risk, studies of nonselective, nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen have been inconsistent.

Methods and Results—We examined the influence of NSAIDs and acetaminophen on the risk of major cardiovascular events (nonfatal myocardial infarction, fatal coronary heart disease, nonfatal and fatal stroke) in a prospective cohort of 70 971 women, aged 44 to 69 years at baseline, free of known cardiovascular disease or cancer, who provided medication data biennially since 1990. During 12 years of follow-up, we confirmed 2041 major cardiovascular events. Women who reported occasional (1 to 21 d/mo) use of NSAIDs or acetaminophen did not experience a significant increase in the risk of cardiovascular events. However, after adjustment for cardiovascular risk factors, women who frequently (≥22 d/mo) used NSAIDs had a relative risk (RR) for a cardiovascular event of 1.44 (95% CI, 1.27 to 1.65) compared with nonusers, whereas those who frequently consumed acetaminophen had a RR of 1.35 (95% CI, 1.14 to 1.59). The elevated risk associated with frequent NSAID use was particularly evident among current smokers (RR=1.82; 95% CI, 1.38 to 2.42) and was absent among never smokers ($P_{interaction}$=0.02). Moreover, we observed significant dose-response relations: Compared with nonusers, the RRs for a cardiovascular event among women who used ≥15 tablets per week were 1.86 (95% CI, 1.27 to 2.73) for NSAIDs and 1.68 (95% CI, 1.10 to 2.58) for acetaminophen.

Conclusions—Use of NSAIDs or acetaminophen at high frequency or dose is associated with a significantly increased risk for major cardiovascular events, although more moderate use did not confer substantial risk. **(*Circulation*. 2006;113: 1578-1587.)**

Key Words: acetaminophen ■ aspirin ■ cardiovascular diseases ■ cyclooxygenase-2 inhibitors ■ nonsteroidal antiinflammatory drugs

Randomized intervention trials suggest that regular use of cyclooxygenase (COX) isoenzyme-2–selective inhibitors is associated with an elevated risk of serious cardiovascular events.[1–3] Traditional, nonaspirin, nonsteroidal antiinflammatory drugs (NSAIDs), such as ibuprofen or naproxen, inhibit COX enzymes less selectively. Whether these agents have a similar effect on cardiovascular risk remains unclear. Recently, investigators halted an Alzheimer disease prevention trial because of an excess of cardiovascular events in participants randomized to naproxen.[4] A study nested in the Norwegian Cancer Registry observed a nearly 3-fold greater risk of cardiovascular deaths among smokers who used ibuprofen.[5] Previous studies of NSAIDs and cardiovascular risk have been inconsistent: Some have observed an increased risk[6–13]; some have shown no effect[14–22]; others have suggested a potential cardioprotective benefit.[23–29] Fewer studies have investigated acetaminophen and cardiovascular events.[30] Nonetheless, acetaminophen and NSAIDs are associated with an increased risk of hypertension,[31–34] and the acetaminophen precursor phenacetin is associated with excess cardiovascular morbidity and mortality.[35]

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On the basis of present understanding of their mechanism of action and these prior studies, we hypothesized that frequent use of NSAIDs and acetaminophen, but not aspirin,

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may be associated with excess cardiovascular risk. Thus, we examined the influence of these analgesics on the risk of cardiovascular events in a large cohort of women enrolled in the Nurses' Health Study. Over a 12-year period, these participants provided detailed and updated information on their use. This prospective cohort study permitted a more comprehensive examination of the effect of these agents over a broader range of intake than would be immediately feasible in a placebo-controlled trial.

Methods

Participants

The Nurses' Health Study was established in 1976 when 121 701 US female registered nurses, aged 30 to 55 years, completed a mailed questionnaire. Follow-up questionnaires have been sent biennially thereafter to ascertain information on risk factors and identify newly diagnosed cardiovascular events and other health outcomes. A validated semiquantitative food-frequency questionnaire was added in 1980 to assess intake of nutrients.[36] In 1990, the questionnaire was expanded to include an assessment of patterns of NSAID and acetaminophen use. The institutional review board at the Brigham and Women's Hospital approved this study; all participants provided informed consent.

Assessment of Medication Use

As previously described,[37] beginning in 1990 we asked women if they regularly used aspirin, other antiinflammatory drugs "(eg, ibuprofen, Naprosyn [Roche Pharmaceuticals, Nutley, NJ], Advil [Wyeth, Madison, NJ])," and acetaminophen "(eg, Tylenol [McNeil Consumer & Specialty Pharmaceuticals, Fort Washington, Pa])," and the frequency of use. We updated these data biennially; beginning in 1998, for each agent, we also asked participants the number of tablets used per week. Early in the study, most women used standard-dose aspirin tablets; however, to reflect overall trends in consumption of low-dose aspirin, questionnaires after 1992 asked participants to convert intake of 4 "baby" aspirin to 1 adult tablet, and in 2000 we inquired specifically about baby or low-dose aspirin. COX-2 inhibitors were not introduced in the United States until 1999; hence, we first asked women in 2000 to report if they regularly used "Celebrex (Pfizer Inc, New York, NY) or Vioxx (Merck & Co Inc, West Trenton, NJ) (COX-2 inhibitors)" but did not inquire specifically about frequency or dose.

In a subsample of 200 women who reported aspirin use in 1990, we conducted a study to determine the reasons for use (91% response). The major reasons for use among women taking 1 to 6 and ≥7 aspirin tablets per week were headache (32% and 18%, respectively); arthritis and other musculoskeletal pain (30% and 50%); a combination of headache and musculoskeletal pain (16% and 15%); cardiovascular disease prevention (9% and 8%); and other reasons (13% and 9%).[38]

In 1999, we also sent a supplementary questionnaire to 4238 of the participants (91% response) to ascertain a 10-year detailed history of analgesic use.[39] Among aspirin users, 67% typically used 1 tablet per day, and 75% typically used tablets >300 mg. Among NSAID users, 73% used ibuprofen, 14% used naproxen, and 13% used other type; 53% typically used 2 tablets per day, 25% used 1 tablet per day, and 22% used ≥3 tablets per day. Among ibuprofen users, 62% reported using tablets between 100 and 299 mg. Among acetaminophen users, 55% typically used 2 tablets per day, 18% used 1 tablet per day, and 26% used ≥3 tablets per day; 69% used tablets of ≥500 mg. The major reasons for use among ibuprofen and acetaminophen users were muscle/joint pain (84% and 65%, respectively); headache (5% and 24%); backache (5% and 4%); and other reasons (6% and 8%).

Ascertainment of Cases

We requested written permission to acquire medical records from women who reported a myocardial infarction or stroke on our biennial questionnaire. We have previously described our methods for confirmation in detail.[38,40] Briefly, we confirmed myocardial infarction if the case met the World Health Organization criteria of symptoms and either typical ECG changes or elevated cardiac enzymes.[41] Infarctions of indeterminate age were excluded. We confirmed stroke according to criteria of the National Survey of Stroke. Myocardial infarctions or strokes that required hospital admission and for which confirmatory information was obtained by personal interview were designated as probable. We included all confirmed and probable cases because results were not substantially different after exclusion of probable cases (data not shown).

We identified deaths through the National Death Index and next of kin.[42] For all deaths attributable to coronary heart disease or stroke, we requested permission from next of kin to review medical records and death certificates. Fatal coronary heart disease was confirmed by records or autopsy or if coronary heart disease was listed as the cause of death on the death certificate and evidence of previous coronary heart disease was available. Fatal stroke was confirmed by medical records, death certificates, or telephone interview with next of kin.

Statistical Analysis

At baseline, we included all women who completed the long version of the 1990 questionnaire that included the medication questions. We excluded women who left the medication questions blank, reported a history of cancer (except nonmelanoma skin cancer), prior myocardial infarction, stroke, coronary artery bypass grafting/percutaneous coronary intervention, or angina. After these exclusions, 70 971 women were eligible for analysis. Person-time for each participant was calculated from the date of return of the 1990 questionnaire to the date of the first nonfatal myocardial infarction, nonfatal stroke, fatal coronary event, fatal stroke, death from any cause, or June 1, 2002, whichever came first. To minimize any potential bias related to either use or avoidance of analgesics related to symptomatic ischemic heart disease, we censored participants who reported coronary artery bypass grafting, percutaneous coronary intervention, or angina during follow-up; these events were not included as end points. In the main analyses, we used Cox proportional hazards modeling to control for multiple variables simultaneously and to compute 95% CIs and used the specific categories of frequency of use of acetaminophen, aspirin, and NSAIDs as detailed in the 1990 and 1992 questionnaires.[33] Some regrouping was required to adjust for different categories in later questionnaires. For each 2-year time period between assessments, we used the most updated information for each analgesic as well as other covariates. In secondary analyses, we also assessed the influence of the number of tablets per week, beginning follow-up with return of the 1998 questionnaire when these data were first collected. We also performed stratified analyses to examine potential interactions. We used SAS version 8.2 (Cary, NC). All probability values were 2 sided.

The authors had full access to the data and take responsibility for its integrity. All authors have read and agree to the manuscript as written.

Results

Among the 70 971 women, we documented 2041 cardiovascular events (814 nonfatal myocardial infarctions, 795 nonfatal strokes, 277 coronary heart disease deaths, and 155 fatal strokes) over 765 626 person-years. Compared with lower-frequency users, women reporting the highest levels of use of each analgesic were older, less likely to exercise regularly, more likely to be hypertensive, and had a higher body mass index and a greater number of cardiac risk factors (Table 1).

For both NSAIDs and acetaminophen, we observed no significant difference in risk of cardiovascular events across categories of use between 1 and 21 d/mo compared with nonusers (Table 2). However, compared with nonusers, women who used NSAIDs frequently (≥22 d/mo) had a significantly elevated risk for a cardiovascular event (age-

TABLE 1. Baseline Characteristics of the Study Cohort in 1990*

	Frequency of Use, d/mo				
	None	1–4	5–14	15–21	≥22
NSAIDs	n=44 843	n=12 989	n=5481	n=1705	n=5953
Mean age, y	57.2	53.9	54.3	55.5	57.8
Mean body mass index, kg/m^2†	24.7	25.0	25.5	26.0	26.7
Physical activity, mean MET/wk‡	16.0	16.0	15.3	14.0	14.4
Mean daily intake§					
Saturated fat, g	18.9	18.9	19.1	19.1	19.0
Folate, μg	425	428	435	441	460
Omega-3 fatty acids, mg	251	260	255	263	260
Alcohol, g	5.1	5.2	5.4	5.3	4.8
Hypertension, %	26.9	26.9	30.8	32.2	38.8
Diabetes mellitus, %	3.7	3.6	4.3	4.8	6.7
Hypercholesterolemia, %	35.0	36.3	38.0	39.9	42.5
Smoking history					
Past, %	37.1	40.5	41.4	41.2	42.2
Current, %	17.2	15.8	16.5	16.2	15.2
Postmenopausal, %‖	77.7	75.7	76.4	79.0	82.0
Past use of hormones, %	16.6	17.6	19.7	17.5	17.7
Current use of hormones, %	36.1	43.1	42.3	45.1	47.9
Parental myocardial infarction, age ≤60 y %	16.4	16.7	17.3	17.2	18.4
Current use					
Aspirin, %	49.2	43.5	41.7	33.2	24.4
Acetaminophen, %	41.4	49.0	46.5	41.8	41.4
Multivitamin, %	33.8	36.4	38.3	39.2	40.4
Cardiac risk factors, No.#					
0, %	37.0	36.7	33.2	29.6	26.2
1, %	37.2	37.1	36.0	37.3	34.7
2, %	19.2	19.4	22.5	24.7	25.9
≥3, %	6.6	6.9	8.3	8.5	13.2
Acetaminophen	n=40 438	n=19 827	n=6178	n=1809	n=2719
Mean age, y	57.1	54.9	55.3	56.4	57.8
Mean body mass index, kg/m^2†	24.8	25.0	25.3	25.6	26.0
Physical activity, mean MET/wk‡	16.3	15.2	14.7	14.8	13.8
Mean daily intake§					
Saturated fat, g	18.9	19.0	19.1	19.2	19.4
Folate, μg	429	425	438	436	458
Omega-3 fatty acids, mg	258	250	240	253	246
Alcohol, g	5.5	4.5	4.8	5.3	5.1
Hypertension, %	27.0	27.8	31.9	35.7	38.2
Diabetes mellitus, %	3.8	4.2	4.1	5.3	5.5
Hypercholesterolemia, %	34.9	37.0	39.1	39.8	40.6
Smoking history					
Past, %	38.2	38.9	39.5	42.7	39.0
Current, %	17.2	15.8	15.9	16.8	19.2
Postmenopausal‖	77.3	76.9	78.3	78.8	81.1
Past use of hormones, %	16.7	17.2	18.1	21.8	18.4
Current use of hormones, %	38.2	39.7	41.2	40.6	42.0
Parental myocardial infarction, age ≤60 y, %	16.6	16.5	17.2	17.7	17.3

TABLE 1. Continued

	Frequency of Use, d/mo				
	None	1–4	5–14	15–21	≥22
Current use¶					
Aspirin, %	52.5	35.6	35.9	30.4	29.4
NSAID, %	35.0	37.5	42.5	44.5	42.1
Multivitamin, %	34.3	35.0	38.4	38.3	43.2
Cardiac risk factors, No.#					
0, %	36.8	35.7	32.1	28.4	28.3
1, %	36.8	37.2	37.1	37.7	33.8
2, %	19.5	19.8	22.6	24.2	25.4
≥3, %	6.9	7.2	8.2	9.7	12.4
Aspirin	n=39 029	n=15 898	n=6395	n=2695	n=6954
Mean age, y	56.1	55.7	56.4	57.5	58.9
Mean body mass index, kg/m^2†	25.0	24.7	25.0	25.4	25.4
Physical activity, mean MET/wk‡	15.6	15.9	16.2	15.6	15.6
Mean daily intake§					
Saturated fat, g	18.9	19.0	19.1	19.0	18.9
Folate, μg	426	422	429	439	467
Omega-3 fatty acids, mg	256	247	249	257	262
Alcohol, g	4.8	5.3	5.5	6.2	5.7
Hypertension, %	27.6	25.6	28.7	33.0	36.2
Diabetes mellitus, %	4.3	3.2	3.3	4.2	5.0
Hypercholesterolemia, %	35.6	34.8	36.4	38.2	41.1
Smoking history					
Past, %	38.7	37.3	39.5	40.1	49.0
Current, %	17.1	15.9	15.2	16.9	19.0
Postmenopausal‖	77.3	76.6	77.6	78.7	81.1
Past use of hormones, %	17.5	15.9	17.4	17.9	17.3
Current use of hormones, %	38.0	39.7	40.4	40.1	41.5
Parental myocardial infarction, age ≤60 y, %	16.2	16.4	16.8	18.8	18.9
Current use¶					
Acetaminophen, %	50.8	37.3	32.9	29.0	26.4
NSAID, %	41.7	31.0	32.9	31.0	28.7
Multivitamin, %	33.2	34.9	38.0	39.7	43.8
Cardiac risk factors, No.#					
0, %	35.7	39.0	36.0	31.1	28.0
1, %	37.2	36.0	37.0	38.7	36.6
2, %	19.7	19.2	20.3	21.4	24.8
≥3, %	7.5	5.9	6.7	8.8	10.6

*Characteristics at baseline questionnaire in 1990. All values, other than age, have been age-standardized according to the age distribution of the cohort.

†The body mass index is the weight in kilograms divided by the square of the height in meters.

‡Metabolic equivalent tasks.

§Nutrient values represent the mean of energy-adjusted intake. Omega-3 fatty acids include n-3 eicosapentaenoic acid and n-3 docosahexaenoic acid.

‖Hormones are defined as postmenopausal estrogen or estrogen/progesterone preparations. Percentage of past and current use was calculated among postmenopausal women only.

¶Current use is defined as intake at least 1 day per month for analgesic categories.

#Cardiac risk factors are hypertension, hypercholesterolemia, diabetes mellitus, current smoking, body mass index ≥30.

adjusted relative risk [RR], 1.67; 95% CI, 1.46 to 1.89). This association was attenuated but remained significant after adjustment for cardiovascular risk factors and the other analgesic classes (multivariate RR, 1.44; 95% CI, 1.27 to 1.65). Moreover, we additionally adjusted for the effect of cardiovascular risk factors such as systolic and diastolic blood pressure and total cholesterol as continuous measures and observed similar associations (data not shown). We found a similar relationship for women using acetaminophen frequently (multivariate RR, 1.35; 95% CI, 1.14 to 1.59). In

TABLE 2. RR of Cardiovascular Events According to Frequency of Analgesic Use, 1990–2002*

	Frequency of Use, d/mo					
	None	1–4	5–14	15–21	≥22	*P* for Trend
NSAIDs						
Person-years	544 472	79 634	52 544	21 079	67 356	
No. of cases	1467	139	104	43	288	
Age-adjusted RR (95% CI)	1.0	0.96 (0.80–1.14)	1.01 (0.82–1.23)	0.98 (0.72–1.32)	1.67 (1.46–1.89)	<0.0001
Multivariate RR† (95% CI)	1.0	0.95 (0.80–1.14)	1.01 (0.82–1.24)	0.92 (0.68–1.25)	1.51 (1.33–1.73)	<0.0001
Multivariate RR‡ (95% CI)	1.0	0.95 (0.79–1.14)	1.00 (0.81–1.22)	0.91 (0.67–1.23)	1.44 (1.27–1.65)	<0.0001
Acetaminophen						
Person-years	546 800	108 179	54 166	20 596	35 344	
No. of cases	1441	221	143	68	168	
Age-adjusted RR (95% CI)	1.0	1.00 (0.87–1.17)	1.19 (1.00–1.42)	1.36 (1.07–1.74)	1.72 (1.47–2.03)	<0.0001
Multivariate RR† (95% CI)	1.0	0.99 (0.85–1.15)	1.12 (0.94–1.33)	1.25 (0.98–1.60)	1.41 (1.19–1.66)	<0.001
Multivariate RR‡ (95% CI)	1.0	0.98 (0.84–1.14)	1.09 (0.91–1.30)	1.22 (0.95–1.56)	1.35 (1.14–1.59)	0.0001
Aspirin						
Person-years	477 859	94 691	53 716	31 794	107 025	
No. of cases	1298	168	111	85	379	
Age-adjusted RR (95% CI)	1.0	0.72 (0.61–0.85)	0.77 (0.64–0.94)	0.92 (0.74–1.15)	1.11 (0.99–1.26)	0.11
Multivariate RR† (95% CI)	1.0	0.80 (0.68–0.94)	0.86 (0.70–1.05)	1.03 (0.82–1.29)	1.13 (1.00–1.27)	0.05
Multivariate RR‡ (95% CI)	1.0	0.80 (0.68–0.95)	0.85 (0.70–1.04)	1.00 (0.80–1.26)	1.07 (0.95–1.20)	0.25

*Cardiovascular events include nonfatal myocardial infarction, nonfatal stroke, fatal coronary heart disease, and fatal stroke. RRs are for women in each frequency category compared with women in the reference category of none.

†Multivariate RRs are adjusted for age, parental history of myocardial infarction before age 60 years (yes or no), history of diabetes mellitus (yes or no), history of hypercholesterolemia (yes or no), smoking history (never, past, current smoker), body mass index (<22, 22–24.9, 25–26.9, 27–29.9, ≥30), regular moderate or vigorous exercise (<1.7, 1.7–4.5, 4.6–10.5, 10.6–22.1, and >22.1 metabolic equivalent task score per week), postmenopausal hormone use (premenopausal, never, past, current), current multivitamin use (yes or no), energy-adjusted quintiles of folate (dietary and supplement), omega-3 fatty acids, saturated fat, alcohol (0, 0.1–4.9, 5.0–14.9, ≥15 g/d), and other analgesic categories.

‡Multivariate RRs are adjusted for aforementioned variables as well as history of hypertension (yes or no).

contrast with NSAIDs and acetaminophen, aspirin was not associated with an elevated risk of cardiovascular events, even in the highest-frequency category (multivariate RR, 1.07; 95% CI, 0.95 to 1.20); there was a modest inverse association with low-frequency aspirin use (multivariate RR, 0.80; 95% CI, 0.68 to 0.95 for 1 to 4 d/mo).

We considered the possibility that chronic inflammatory diseases associated with elevated cardiovascular risk as well as analgesic use may have influenced our results. However, controlling for such conditions did not materially alter our results. Compared with nonusers of each agent, the RR for frequent users of NSAIDs was 1.40 (95% CI, 1.22 to 1.60), and the RR for frequent users of acetaminophen was 1.33 (95% CI, 1.13 to 1.57), after adding history of gout, osteoarthritis, and rheumatoid arthritis to our multivariate model. Furthermore, the effect of NSAIDs and acetaminophen did not differ according to the presence or absence of these chronic conditions. Among women without gout, osteoarthritis, or rheumatoid arthritis, the multivariate RR was 1.66 (95% CI, 1.23 to 2.23) for frequent NSAID use and 1.30 (95% CI, 0.92 to 1.85) for frequent acetaminophen use. Among women with at least 1 of these conditions, the multivariate RR was 1.33 (95% CI, 1.14 to 1.56) for frequent NSAID use and 1.33 (95% CI, 1.10 to 1.62) for frequent acetaminophen use.

Previous data demonstrate that both NSAIDs and acetaminophen are independently associated with an elevated risk of hypertension.[32,33] Thus, we considered the possibility that the effect of these agents on cardiovascular risk may be mediated through this mechanism and adjustment for hypertension in our multivariate models may minimize a potential association. After adjusting for all cardiovascular risk factors except hypertension, we found that the multivariate RRs for women taking these agents frequently were, in fact, generally stronger (RR, 1.51; 95% CI, 1.33 to 1.73 for NSAIDs; RR, 1.41; 95% CI, 1.19 to 1.66 for acetaminophen; Table 2).

We also evaluated the influence of these agents on specific coronary heart disease end points (Table I in the online-only Data Supplement). For women who frequently used NSAIDs or acetaminophen, we observed a consistently elevated risk for nonfatal myocardial infarction, fatal coronary heart disease, and all coronary heart disease end points (multivariate RR, 1.58; 95% CI, 1.32 to 1.89 for NSAIDs; multivariate RR, 1.56; 95% CI, 1.26 to 1.93 for acetaminophen). However, aspirin was not associated with a significantly elevated risk of any coronary heart disease.

Similarly, women who reported NSAID use ≥22 d/mo experienced a significantly greater risk for stroke (multivariate RR, 1.29; 95% CI, 1.06 to 1.57; Table II in the online-only Data Supplement), although the risk associated with acetaminophen was somewhat attenuated. In contrast, frequent aspirin users did not experience any increased risk of stroke; moreover, low-frequency users had a significant

reduction in risk of stroke (multivariate RR, 0.72; 95% 0.56 to 0.93).

In 1998, participants reported the number of tablets per week as well as frequency. In secondary analyses, we examined the influence of tablets per week with follow-up beginning with return of the 1998 questionnaire (Table 3). For both NSAIDs and acetaminophen, the risk appeared to be related to increasing dose. Compared with participants who took no NSAIDs, the multivariate RR for women who used ≥15 tablets per week was 1.86 (95% CI, 1.27 to 2.73; *P* for trend≤0.001). Similarly, for acetaminophen, women who reported ≥15 tablets per week experienced a RR of 1.68 (95% CI, 1.10 to 2.58; *P* for trend=0.002). In contrast, neither increasing frequency of aspirin use nor increasing aspirin dose was associated with elevated risk of cardiovascular events.

Although the vast majority of NSAID users in the study used ibuprofen, we considered the possibility that other types of NSAIDs might have a differential influence on risk of cardiovascular events. Beginning in 1998, we first asked participants if they regularly used a NSAID other than ibuprofen at least 2 times a week. Among regular users of nonibuprofen NSAIDs, we observed a multivariate RR of 1.62 (95% CI, 1.21 to 2.15) compared with women who did not regularly use nonibuprofen NSAIDs.

The influence of NSAIDs and acetaminophen on cardiovascular disease was not significantly modified by participant age; aspirin use; body mass index; physical activity; or presence or absence of hypertension, hypercholesterolemia, or diabetes mellitus. The risk associated with frequent NSAID use appeared to be influenced by smoking status (*P* for interaction=0.02). Frequent use of NSAIDs was associated with a multivariate RR of 1.82 (95% CI, 1.38 to 2.42) among current smokers, 1.58 (95% CI, 1.28 to 1.95) among past smokers, and 1.11 (95% CI, 0.88 to 1.41) among nonsmokers. In contrast, smoking did not appear to influence the effect of acetaminophen on risk (*P* for interaction=0.97).

Because COX-2–selective inhibitors are associated with elevated cardiovascular risk, we also considered the possibility that differential use of these agents among frequent NSAID and acetaminophen users may have accounted for our findings. Thus, we conducted analyses in which we restricted follow-up through January 1, 1999, before COX-2–selective agents became available for widespread use. Our results remained essentially unchanged; the multivariate RR was 1.44 (95% CI, 1.25 to 1.65) for frequent NSAID use and 1.29 (95% CI, 1.08 to 1.54) for frequent acetaminophen use. In 2000, we first asked participants to report any use of COX-2–selective agents. In an analysis in which we excluded the 5202 participants who reported any use of COX-2–selective agents, we observed a multivariate RR of 1.45 (95% CI, 1.26 to 1.65) for frequent NSAID use and 1.35 (95% CI, 1.14 to 1.59) for frequent acetaminophen use. We evaluated the independent effect of COX-2 inhibitors with follow-up beginning with return of the 2000 questionnaire. Although we found an elevated risk of cardiovascular events among regular users of COX-2 inhibitors (age-adjusted RR, 1.72; 95% CI, 1.10 to 2.69), this was attenuated after multivariate adjustment (RR, 1.47; 95% CI, 0.93 to 2.33). Nonetheless, given the very limited follow-up and statistical power for the analysis of COX-2 inhibitor use, these results must be viewed as preliminary.

Discussion

In this large, prospective study, frequent (≥22 d/mo) use of either NSAIDs or acetaminophen was associated with a modest, although significant, elevated risk of cardiovascular events. This risk appeared to be dose related, with the greatest risk associated with use of ≥15 tablets per week.

Our results extend previous findings suggesting a relationship between use of NSAIDs and cardiovascular events. Three placebo-controlled trials have demonstrated an increased risk of serious cardiovascular events in participants randomized to COX-2 inhibitors.[1–3] An interim analysis of an Alzheimer disease prevention trial suggested similar risk with naproxen, although the full data have not been released.[4] Among users of various types of NSAIDs, a United Kingdom study observed a 20% to 30% elevated risk of myocardial infarction, and a Danish registry study found a 50% to 70% increased risk of hospitalization for myocardial infarction.[11,12] Ibuprofen has been associated with a nearly 2-fold higher risk of cardiovascular mortality in patients prescribed low-dose aspirin after hospitalization for cardiovascular disease.[7] A secondary analysis of the Physicians' Health Study showed a nearly 3-fold higher risk of myocardial infarction associated with NSAIDs in participants randomized to the aspirin arm.[8] NSAIDs have also been associated with an increased risk for congestive heart failure.[9,13] Finally, in a recent case-control study, recent use of any NSAID (including COX-2 inhibitors) and current use of naproxen were associated with a modestly elevated risk of serious coronary heart disease.[10]

Our findings might appear to contrast with prior studies that have observed either no relationship or an inverse association between NSAIDs and cardiovascular events. However, some of these studies were confined to patients with preexisting coronary heart disease,[17,23] rheumatoid arthritis,[26] or elderly individuals.[18] Other analyses were based largely on case-control studies that utilized prescription data, were not able to fully adjust for a range of cardiovascular risk factors, relied on participant recall after a cardiovascular event, assessed only a single measure of analgesic use, or did not differentiate high-frequency from occasional use.[15–18,20–27,29] In fact, our findings of a null relationship in the low- and moderate-frequency categories are consistent with such studies. Finally, although a meta-analysis concluded that certain NSAIDs, such as naproxen, may be associated with a potential cardioprotective benefit,[28] more recent studies, including data presented here, have not confirmed this finding.[10–12]

Our findings for NSAIDs are biologically plausible. NSAIDs inhibit antithrombotic prostacyclins to an extent similar to that of COX-2–selective inhibitors.[43] Although nonselective NSAIDs also inhibit COX-1, which synthesizes the prothrombotic thromboxane A_2, the relative balance between COX-1 and COX-2 activity is critical for vascular homeostasis. All NSAIDs may shift the equilibrium toward thrombosis and vasoconstriction.[44]

TABLE 3. RR of Cardiovascular Events According to Analgesic Frequency and Dose, 1998–2002*

	No. of Cases/Total No. of Person-Years	Age-Adjusted RR (95% CI)	Multivariate RR† (95% CI)
NSAIDs			
Days per week			
None	327/136 700	1.0	1.0
1	22/12 307	1.04 (0.67–1.60)	1.04 (0.67–1.62)
2–3	34/15 710	1.17 (0.82–1.67)	1.15 (0.80–1.66)
4–5	20/7239	1.48 (0.94–2.34)	1.33 (0.84–2.11)
≥6	71/18 767	1.68 (1.30–2.18)	1.51 (1.16–1.98)
P for trend		<0.0001	0.002
Tablets per week‡			
None	326/137 863	1.0	1.0
1–2	20/11 655	1.00 (0.64–1.58)	1.00 (0.63–1.59)
3–5	16/10 088	0.85 (0.51–1.41)	0.82 (0.49–1.37)
6–14	56/18 285	1.47 (1.10–1.95)	1.35 (1.00–1.81)
≥15	31/7550	2.09 (1.44–3.04)	1.86 (1.27–2.73)
P for trend		<0.0001	<0.001
Acetaminophen			
Days per week			
None	326/144 389	1.0	1.0
1	24/13 202	0.94 (0.62–1.42)	0.94 (0.62–1.44)
2–3	48/15 714	1.39 (1.02–1.89)	1.28 (0.94–1.75)
4–5	26/6689	1.66 (1.10–2.48)	1.49 (0.99–2.24)
≥6	50/10 728	1.77 (1.31–2.40)	1.50 (1.10–2.04)
P for trend		<0.0001	0.001
Tablets per week‡			
None	326/144 403	1.0	1.0
1–2	30/13 521	1.15 (0.79–1.67)	1.19 (0.81–1.76)
3–5	27/9692	1.23 (0.83–1.83)	1.16 (0.76–1.76)
6–14	45/12 873	1.55 (1.13–2.12)	1.47 (1.06–2.03)
≥15	25/4796	1.97 (1.29–3.00)	1.68 (1.10–2.58)
P for trend		<0.0001	0.002
Aspirin			
Days per week			
None	244/99 902	1.0	1.0
1	47/19 765	0.91 (0.66–1.25)	1.00 (0.73–1.39)
2–3	22/12 498	0.70 (0.45–1.09)	0.77 (0.50–1.20)
4–5	27/10 878	0.89 (0.59–1.33)	0.95 (0.63–1.43)
≥6	134/47 678	0.96 (0.78–1.19)	0.95 (0.76–1.18)
P for trend		0.20	0.57
Tablets per week‡			
None	250/106 020	1.0	1.0
1–2	57/29 116	0.71 (0.53–0.95)	0.78 (0.58–1.06)
3–5	57/23 484	0.91 (0.68–1.22)	0.96 (0.71–1.29)
6–14	81/23 743	1.15 (0.89–1.48)	1.09 (0.83–1.42)
≥15	10/3291	1.10 (0.58–2.10)	1.11 (0.58–2.11)
P for trend		0.18	0.41

*RRs are for women in each frequency category compared with women in the reference category of none.

†Adjustments as in multivariate model including hypertension, Table 2.

‡Twenty-five cases were missing data on NSAID tablets per week, 21 cases were missing data on acetaminophen tablets per week, 19 cases were missing data on aspirin tablets per week.

In our cohort, the increased risk of cardiovascular events associated with frequent NSAID use was markedly enhanced by cigarette smoking, which may potentiate platelet aggregation.[45] A case-control study of smokers in Norway observed a 2-fold higher risk of cardiovascular death among NSAID users and a nearly 3-fold higher risk among ibuprofen users.[5] Although we did not observe a significant interaction between NSAIDs and aspirin, our findings are consistent with a recent randomized trial of low-dose aspirin and risk of cardiovascular events in women.[46] That trial also failed to detect a significant interaction between concomitant NSAID use and the influence of aspirin; nonetheless, whereas aspirin was associated with a significantly reduced risk of cardiovascular events among nonsmokers, aspirin conferred a significant increase in risk (RR=1.30) among current smokers.[46]

Data examining the influence of acetaminophen on cardiovascular risk are comparatively sparse. A hospital-based case-control study observed a possible inverse association of long-term regular acetaminophen use with first myocardial infarction. However, the study was limited to men aged <55 years, and the observation was based on only 31 cases, was not statistically significant, and was attenuated after excluding subjects who reported angina symptoms.[30] The acetaminophen precursor phenacetin has been strongly associated with analgesic nephropathy as well as excess cardiovascular morbidity and mortality.[35] Furthermore, acetaminophen is associated with a dose-dependent risk of renal insufficiency,[47] an independent predictor of cardiovascular events.[48,49] Two previous prospective studies, including a study of participants in the present cohort, found an association between both acetaminophen and NSAIDs and incident hypertension.[32,33] In a recent analysis of women who provided more extensive data on analgesic usage, a significant, dose-dependent increase in risk of hypertension was observed among women using acetaminophen and NSAIDs irrespective of the reason for their use.[50] A randomized crossover study observed a significant rise in systolic blood pressure with short-term acetaminophen use.[31] Although only weakly inhibiting COX-1 and COX-2,[51] acetaminophen also inhibits prostaglandin production[52] and may impair endothelial function through depletion of glutathione.[53] Recent findings suggest that acetaminophen may mediate some of its effects through inhibition of a splice variant of COX-1, also known as COX-3.[51]

We observed a significant yet modestly protective benefit of aspirin use in the low-frequency categories (1 to 14 d/mo) on risk of stroke but not coronary heart disease. This dose range is consistent with present understanding about the minimum effective dose needed to fully inhibit thromboxane production.[54] Our findings are also consistent with the results of a recent randomized controlled trial of alternate-day, low-dose aspirin in healthy women that similarly demonstrated a significant reduction in stroke but not myocardial infarction.[46]

Our study had several strengths. First, we collected detailed information on analgesics from a large number of participants, permitting an investigation of use across a broader range of intake. Second, because we asked distinct questions about aspirin, NSAIDs, and acetaminophen, we were able to examine these drugs individually. Third, we obtained analgesic data prospectively, before diagnosis. Thus, any errors in recall would have tended to attenuate rather than exaggerate true associations, and any biases related to incomplete data collection from participants with fatal diagnoses were minimized. Fourth, to account for changes in participants' patterns of use over several years, we updated analgesic data biennially and used the most recent exposure and risk factor data for each 2-year time period. Finally, although studies that utilize prescription records have provided important data on the influence of prescription medications, our cohort of registered nurses likely provides more accurate data on actual consumption of over-the-counter medications, such as NSAIDs and acetaminophen. Furthermore, we collected more detail on cardiovascular risk factors, comorbid inflammatory conditions, and other potential confounders than typically available from large administrative databases.

Several limitations of our study deserve comment. Our study was observational, and analgesic use was self-selected. Thus, despite the strong biological plausibility of our results, it is possible that our findings could be related to the reason for which participants used NSAIDs or acetaminophen. However, high doses of these agents, including aspirin, were primarily used for analgesia,[38] and we did not find an increased risk of cardiovascular events among high-frequency aspirin users. Although we cannot completely exclude residual confounding by factors associated with frequent analgesic intake, our findings remained significant even after carefully controlling for known cardiovascular risk indicators as well as common reasons for chronic analgesic use, including gout, osteoarthritis, and rheumatoid arthritis. Additionally, when we stratified participants according to the presence or absence of these chronic conditions, our results remained largely unchanged. We also censored participants with angina or who underwent coronary revascularization, minimizing any potential protopathic bias related to analgesic intake for cardiovascular symptoms. Nevertheless, the strong evidence of increased cardiovascular risk among frequent NSAID or acetaminophen users, whether entirely attributable to the pharmacological consequences of the drugs, is of interest in itself.

The observational design of our study does not permit us to assign causality as would a randomized intervention trial designed to evaluate the effect of analgesics on cardiovascular risk. However, such a trial may not be feasible given the need for a large number of participants and prolonged follow-up, as well as ethical concerns given the findings from the COX-2 trials. As a result, some authorities have supported the use of an observational study such as ours to provide a timely and efficient assessment of drug safety.[55]

Our findings could have a substantial overall impact on public health. Concerns over the safety of COX-2–selective inhibitors will likely result in a decline in use of these agents in favor of traditional NSAIDs or acetaminophen. Ultimately, our results support the value of either long-term clinical trials or postmarketing surveillance of chronically used medications, including drugs that have been in long-standing clinical practice. Moreover, our findings support recommendations that long-term use of analgesics, including over-the-counter

drugs, should be undertaken in consultation with a physician.[56]

In summary, we did not observe a significantly elevated risk in cardiovascular events with less than daily use of NSAIDs and acetaminophen. However, use of NSAIDs or acetaminophen at high frequency or dose was associated with an increased risk, particularly among current smokers. Our results suggest the importance of carefully evaluating the ongoing use of analgesic agents and weighing their benefits with potential risks.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Concerns over the cardiovascular safety of cyclooxygenase-2 (COX-2)–selective inhibitors will likely result in a decline in use of these agents in favor of traditional, nonselective, nonsteroidal antiinflammatory drugs (NSAIDs) or acetaminophen. However, it remains unclear whether these analgesics may also be associated with cardiovascular risk. Thus, we examined the influence of NSAIDs and acetaminophen on the risk of major cardiovascular events (nonfatal myocardial infarction, nonfatal stroke, fatal coronary heart disease, and fatal stroke) in a prospective cohort of 70 971 women, aged 44 to 69 years at baseline, with no prior history of cardiovascular disease or cancer, who provided data on medication use biennially since 1990. During 12 years of follow-up, we confirmed 2041 major cardiovascular events. Women who reported less than daily use of NSAIDs or acetaminophen (1 to 21 d/mo) did not experience a significant increase in the risk of cardiovascular events. However, after adjustment for a variety of cardiovascular risk factors, frequent (≥22 d/mo) use of either NSAIDs or acetaminophen was associated with a modest, although significant, elevated risk of cardiovascular events, particularly among current smokers. This risk appeared to be dose related, with the greatest risk associated with use of ≥15 tablets per week. In contrast, frequent use of aspirin was not associated with excess cardiovascular risk. Our results support the importance of either long-term clinical trials or postmarketing surveillance of chronically used medications, including drugs that have been in long-standing clinical practice. Moreover, our findings support recommendations that long-term use of analgesics, including over-the-counter drugs, should be undertaken in consultation with a physician.