Acetaminophen Use and Risk of Myocardial Infarction and Stroke in a Hypertensive Cohort

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Abstract—Recent data suggest that self-reported acetaminophen use is associated with increased risk of cardiovascular events and that acetaminophen causes a modest blood pressure rise. There are no randomized trials or studies using verified prescription data of this relationship. We aimed to assess the relationship between verified acetaminophen prescription data and risk of myocardial infarction or stroke in patients with hypertension. We performed a retrospective data analysis using information contained within the UK Clinical Research Practice Datalink. Multivariable Cox proportional hazard models were used to estimate hazard ratios for myocardial infarction (primary end point), stroke, and any cardiovascular event (secondary end points) associated with acetaminophen use during a 10-year period. Acetaminophen exposure was a time-dependent variable. A propensity-matched design was also used to reduce potential for confounding. We included 24 496 hypertensive individuals aged ≥65 years. Of these, 10 878 were acetaminophen-exposed and 13 618 were not. There was no relationship between risk of myocardial infarction, stroke, or any cardiovascular event and acetaminophen exposure on adjusted analysis (hazard ratio, 0.98; 95% confidence interval, 0.76–1.27; hazard ratio, 1.09; 95% confidence interval, 0.86–1.38; and hazard ratio, 1.17; 95% confidence interval, 0.99–1.37; respectively). Results in the propensity-matched sample (n=4000 per group) and when men and women were analyzed separately were similar. High-frequency users (defined as receiving a prescription for >75% of months) were also not at increased risk. After allowance for potentially confounding variables, the use of acetaminophen was not associated with an increased risk of myocardial infarction or stroke in a large cohort of hypertensive patients. **(*Hypertension*. 2015;65:1008-1014. DOI: 10.1161/HYPERTENSIONAHA.114.04945.)** ● **Online Data Supplement**

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Acetaminophen is the most widely used analgesic and the initial drug of choice for treatment of chronic pain.[1] Acetaminophen is preferred particularly in those with increased cardiovascular risk after concerns about the cardiovascular safety of nonsteroidal anti-inflammatory drugs (NSAIDs) and selective inhibitors of cyclo-oxygenase (COX)-2.[2,3] However, recent data suggest that acetaminophen also inhibits COX-2[4] via a peroxidase site on prostaglandin H2 synthase[5] and may have a central action on a further COX variant.[6]

The increased cardiovascular risk associated with the use of nonsteroidal anti-inflammatory drugs[1–3] is most apparent for the more COX-2 selective drugs. This may be mediated by an increase in blood pressure because of the renal inhibitory effects of COX-2 inhibition and reduced prostacyclin production in the vasculature to yield a prothrombotic state via unopposed action of thromboxane. Whether acetaminophen has similar actions is unknown but a recent small, randomized, placebo-controlled crossover study found that acetaminophen increased systolic and diastolic blood pressures by 3 and 2 mm Hg, respectively.[7] In women, self-reported frequent acetaminophen use has been associated with increased risk of major cardiovascular events of a similar magnitude to that after frequent NSAID use.[8] Because of the cardiovascular safety of acetaminophen is now being questioned, rigorous evaluation of any associated cardiovascular risk is warranted. Thus, we investigated the relationship between acetaminophen use and the occurrence of myocardial infarction and stroke in high-risk patients, a hypertensive cohort using data contained in the UK Clinical Practice Research Datalink (CPRD).[9]

Methods

The CPRD (formerly the UK General Practice Research Database), described in detail elsewhere,[9] is the largest longitudinal database of

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medical records in the world and contains details of demographic characteristics, medical history, prescriptions, medical diagnoses, and referrals to secondary care. This resource currently holds data on >5 million patients from 590 General Practices throughout the United Kingdom. The demographic profile of the CPRD is representative of the national population[10] and the validity of its data has been confirmed.[11]

Approval for the study was granted by the Independent Scientific Advisory Committee of the General Practice Research Database/CPRD and access to the database was funded via a license agreement with the UK Medical Research Council. Ethical approval for all purely observational studies using General Practice Research Database/CPRD data has been granted by the National Research Ethics Service.

Study Cohort

The data extract provided by the CPRD included all patients aged ≥65 years with a diagnosis of hypertension, who were registered in the CPRD on January 1, 1996 (the date of cohort entry), with at least 2 years of validated follow-up before this date. This age range was selected because, from age 65 years, patients in the United Kingdom do not pay prescription charges, thus minimizing the risk of confounding by overthe-counter use of acetaminophen. Hypertension was defined as a documented record of hypertension within the 10 years before cohort entry or ≥2 blood pressure readings of >160/90 mm Hg within the same period. Patients with a prior diagnosis of chronic kidney disease, asthma, chronic obstructive pulmonary disease, and rheumatoid arthritis were excluded. After these inclusion and exclusion criteria were applied, the CPRD extract included 44 406 individuals (Figure 1).

Assessment of Acetaminophen Exposure and Relevant Concomitant Medication

Acetaminophen is known as paracetamol in the United Kingdom. Acetaminophen use was therefore defined as ≥3 prescriptions for any paracetamol or paracetamol-containing preparation after the date of cohort entry. These drugs were identified as those included in the British National Formulary classification 4.7.1. The number of prescriptions and dates of each prescription were extracted. A patient was classed as paracetamol-exposed if they had received ≥3 prescriptions for paracetamol, with a recorded prescription date within the study period. Patients were classed as nonexposed if they had no record or recorded date of paracetamol prescriptions (therefore patients with a record of paracetamol prescription without an associated date for all or with 1 or 2 paracetamol prescriptions were excluded from both groups).

We defined users as high frequency if they received prescriptions for ≥75% months leading up to censoring or an end point event, medium if they received prescriptions for between 26% and 74% of months and low if they received prescriptions in ≤25% months.

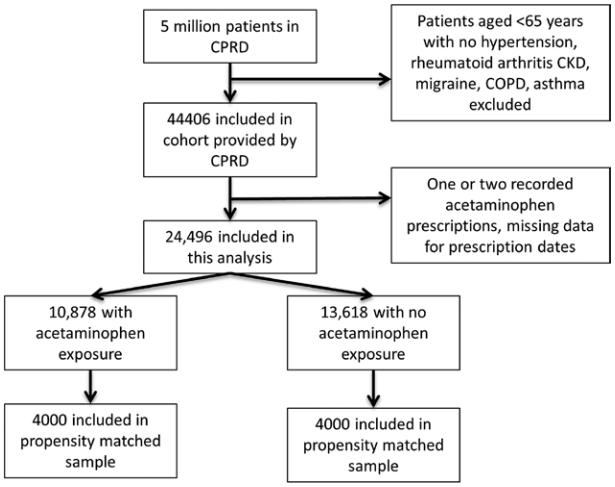

Figure 1. Flow chart of patients included in the analysis. CKD indicates chronic kidney disease; and CPRD, Clinical Practice Research Datalink.

Use of NSAID drugs, with the exception of aspirin (which is not thought to have selective COX-2 or hypertensive effects[12]), was defined similarly using the British National Formulary classification 10.1.1. We defined use of aspirin and HMG CoA (3-hydroxy-3-methyl-glutaryl-CoA) reductase inhibitors using British National Formulary codes (2.9 and 2.12, respectively).

Outcomes of Interest

The primary outcome was occurrence of a myocardial infarction (MI) before January 1, 2006, giving a 10-year follow-up period. Stroke (defined as either ischemic or hemorrhagic) and occurrence of any major cardiovascular event (defined as MI, stroke, transient ischemic attack, coronary artery bypass grafting, carotid endarterectomy, major limb amputation, or surgical embolectomy) before January 1, 2006 were secondary end points. Both fatal and nonfatal events were considered. Only the first event during the follow-up period was included in the analysis. The occurrence of each event was defined by presence of at least 1 compatible and prespecified diagnostic Read/Oxford Medical Information System code. The date of record entry was defined as the date of the event. Patients were censored on January 1, 2006 or on the date of their last recorded follow-up.

Statistical Analysis

Differences between the acetaminophen-exposed and non–acetaminophen-exposed patients were assessed using a 2-sample test for continuous variables and a χ^2 test for dichotomous variables. The risk associated with acetaminophen exposure was assessed using Cox proportional hazard model treating acetaminophen as a time-dependent covariate. This was performed using Proc Phreg in SAS (version 9.3; SAS Institute) and considering a subject as exposed to acetaminophen or not exposed to acetaminophen across all months in the study based on the dates of each prescription. Relevant baseline covariates were accounted for in adjusted analysis and included blood pressure level, medication use, and baseline characteristics. First, we assessed risk of MI (primary outcome) and then stroke and any cardiovascular event (secondary outcomes). We assessed whether there was an interaction between sex and acetaminophen exposure and then assessed associated risks in men and women separately.

We then used propensity score matching as a further means to limit potential for confounding. A random sample of 4000 subjects was taken from the acetaminophen group and then matched to the same number from the nonexposed reference group. This was performed using nearest neighbor matching using clinically relevant baseline covariates in the matching process. All propensity score matching was performed using the MatchIt package in R (version 2.12.2; Vienna, Austria). Cox proportional hazards models were then applied (as described above) to the matched data set for the primary and secondary outcomes.

Finally, we assessed the risk of primary and secondary outcomes separately in high-, medium-, and low-frequency users. Propensity matching (as described above) was used to identify a control population for comparison to each of the high-, medium-, and low-use groups.

Results

From the total population of 44 406 individuals extracted from the CPRD, 24 496 were included in the main analysis (Figure 1). Patients were excluded because they had either 1 or 2 acetaminophen prescriptions (n=7906) or had insufficient prescription date to assign exposure status by month or nonexposed status (n=12 004). Of the included patients, 10 878 were acetaminophen-exposed and 13 618 were not (the reference group). There were differences between the acetaminophen-exposed and nonexposed patients in several baseline factors (Table 1). For many variables (age, body mass index, smoking status, and peripheral vascular disease), these differences were small (either <1 U for continuous variables or 1% for proportions). The acetaminophen-exposed group had more women, a higher proportion with

Table 1. Baseline Demographic Variables in Acetaminophen-Exposed and Acetaminophen Nonexposed Patients

Variables	Acetaminophen Exposure		*P* Value	All
	No (n=10 878)	Yes (n=13 618)		
Age, y, mean (SD)/n	74.3 (6.8)/13 618	73.3 (6.0)/10 878	<0.0001	73.9 (6.5)/24 496
BMI, mean (SD)/n	26.0 (4.24)/10 119	26.6 (4.3)/8491	<0.0001	26.3 (4.3)/18 610
SBP base, mean (SD)/n	159.1 (21.2)/13 103	158.8 (20.5)/10 493	0.2970	159.0 (20.9)/23 596
DBP base, mean (SD)/n	86.8 (10.3)/13 103	86.6 (9.9)/10 493	0.1790	86.7 (11.1)/23 596
Sex, women, n (%)	7477 (54.9%)	6464 (59.4%)	<0.0001	13941 (56.9%)
Smoking status, yes, n (%)	1694 (12.4%)	1248 (11.5%)	0.0032	2942 (12.0%)
Diabetes mellitus, yes, n (%)	2345 (17.2%)	2605 (23.9%)	<0.0001	4950 (20.2%)
IHD, yes, n (%)	2816 (20.7%)	2065 (19.0%)	0.0010	4881 (19.9%)
PVD, yes, n (%)	301 (2.2%)	170 (1.6%)	0.0002	471(1.9%)
Stroke, yes, n (%)	1858 (13.6%)	1065 (9.8%)	<0.0001	2923 (11.9%)
Relevant statin exposure, yes, n (%)	1791 (13.2%)	2512 (23.1%)	<0.0001	4303 (17.6%)
Relevant NSAID exposure, yes, n (%)	5131 (37.7%)	6577 (60.5%)	<0.0001	11708 (47.8%)
Relevant aspirin exposure, yes, n (%)	4215 (30.95%)	4792 (44.1%)	<0.0001	9007 (36.8%)
NSAID no aspirin exposure, yes, n (%)	917 (6.7%)	1785 (16.4%)	<0.0001	2702 (11.0%)
NSAID and aspirin exposure, yes, n (%)	4214 (30.9%)	4792 (44.1%)	<0.0001	9006 (36.8%)

BMI indicates body mass index; DBP, diastolic blood pressure; IHD, ischemic heart disease; NSAID, nonsteroidal anti-inflammatory drug; PVD, peripheral vascular disease; and SBP, systolic blood pressure.

diabetes mellitus, fewer with previous ischemic heart disease or stroke diagnosis, and higher rates of statin, aspirin, and NSAID exposure. Baseline blood pressure was the same.

The mean follow-up duration was 6.4 years (SD, 3.7). A total of 1790 (7.3%) had an MI, 2132 (8.7%) a stroke, and 4490 (18.3%) had any cardiovascular event.

Acetaminophen Exposure

Of the 10 878 exposed, 276 (2.5%) were high users, 1250 (11.5%) were medium users, and 9352 (86.0%) were low users. High users received a mean of 36.9 (SD, 28.7) acetaminophen prescriptions, medium users a mean of 34.3 (SD, 19.2) prescriptions, and low users received a mean of 8.9 (SD, 6.1) prescriptions. Event rates differed across exposure groups (Table S1 in the online-only Data Supplement) and were highest in high-frequency users.

Propensity Matching

A total of 4000 acetaminophen-exposed and 4000 acetaminophen nonexposed patients were included in the main propensity-matched sample. Groups were well matched with the exception of diagnosis of ischemic heart disease, which was 4% higher in nonexposed patients (Table 2). The proportions of high, medium, and low users corresponded to that in the overall acetaminophen-exposed group. These groups were also well matched (Tables S2–S10).

Acetaminophen Use and Risk of Myocardial Infarction

There was no significant relationship between risk of MI and acetaminophen exposure on unadjusted analysis in either the whole cohort (hazard ratio [HR], 1.08; 95% confidence interval [CI], 0.87–1.32) or the propensity-matched sample (HR, 0.82; 95% CI, 0.55–1.21). Similarly, there was no relationship on adjusted analysis (in either the whole cohort, Table 3, or the propensity-matched sample, Table 4).

Acetaminophen Use and Risk of Stroke

There was no significant relationship between risk of stroke and acetaminophen exposure on the unadjusted analysis in the whole cohort (HR, 1.13; 95% CI, 0.92–1.37) but there was an increased risk of stroke with acetaminophen exposure in the propensity-matched sample (HR, 1.47; 95% CI, 1.10–1.98). However, no significant difference was seen on adjusted analysis in either the whole cohort (Table 3) or the propensity-matched sample (Table 4).

Acetaminophen Use and Risk of Any Cardiovascular Event

On unadjusted analysis, acetaminophen exposure was associated with a higher risk of any cardiovascular event in both the whole cohort (HR, 1.19; 95% CI, 1.04–1.35) and the propensity-matched sample (HR, 1.23; 95% CI, 1.03–1.58). There was no significant difference after adjustment for potential confounding variables in either the whole cohort (Table 3) or the propensity-matched sample (Table 4).

Risk in Men and Women

There was no interaction between sex and acetaminophen exposure for MI (P=0.860), stroke (P=0.971), or any cardiovascular event (P=0.522). There was no relationship between acetaminophen use and any end point when men (n=10 555) and women (n=13 941) were considered separately (Tables S11–S14).

Risk and Frequency of Acetaminophen Use

There was no relationship between acetaminophen use and risk of any of the primary or secondary end points in the

Table 2. Baseline Demographic Variables in Acetaminophen-Exposed and Acetaminophen Nonexposed Patients Included in the Propensity-Matched Analysis

Variables	Acetaminophen Exposure		*P* Value	All
	No (n=4000)	Yes (n=4000)		
Age, y, mean (SD)/n	73.3 (6.3)	73.27 (6.0)	0.9217	73.3 (6.0)/8000
BMI, mean (SD)/n	26.2 (4.3)/3067	26.46 (4.1)/3136	0.0227	26.3 (4.2)/6203
SBP base, mean (SD)/n	158.4 (20.7)/3849	159.06 (20.9)/3866	0.1697	158.7 (20.8)/7715
DBP base, mean (SD)/n	86.5 (10.1)/3849	86.85 (9.9)/3866	0.0771	86.7 (10.0)/7715
Sex, men, n (%)	2350 (58.8%)	2368 (59.2%)	0.6824	4718 (59.0%)
Smoking status, yes, n (%)	450 (11.3%)	459 (11.5%)	0.9884	909 (11.4%)
Diabetes mellitus, yes, n (%)	958 (24.0%)	957 (23.9%)	0.9791	1915 (24.0%)
IHD, yes, n (%)	913 (22.8%)	754 (18.9%)	<0.0001	1667 (20.9%)
PVD, yes, n (%)	80 (2.0%)	66 (1.7%)	0.2423	146 (1.8%)
Stroke, yes, n (%)	535 (13.4%)	412 (10.3%)	<0.0001	947 (11.9%)
Relevant statin exposure, yes, n (%)	929 (23.2%)	941 (23.5%)	0.7512	1870 (23.4)
Relevant NSAID exposure, yes, n (%)	2431 (60.8%)	2426 (60.7%)	0.9089	4857 (60.7%)
Relevant aspirin exposure, yes, n (%)	1774 (44.4%)	1766 (44.2%)	0.8571	3540 (44.3)
NSAID no aspirin exposure, yes, n (%)	657 (16.4%)	660 (16.5%)	0.9279	1317 (16.5%)
NSAID and aspirin exposure, yes, n (%)	1774 (44.4%)	1766 (44.2%)	0.8571	3540 (44.3%)

BMI indicates body mass index; DBP, diastolic blood pressure; IHD, ischemic heart disease; NSAID, nonsteroidal anti-inflammatory drug; PVD, peripheral vascular disease; and SBP, systolic blood pressure.

low, medium, or high-frequency users on unadjusted analysis (online-only Data Supplement). The risk of any cardiovascular event was lower after adjustment in medium-frequency acetaminophen users compared with the reference group (HR, 0.75; 95% CI, 0.59–0.95). No other differences were seen (online-only Data Supplement). The exposed and nonexposed patients were well matched in the high- and medium-frequency analysis (Tables S2–S10).

Discussion

This analysis using one of the world's largest clinical research databases found that acetaminophen use was not associated with an increased risk of MI or stroke in a well-defined cohort with hypertension across all conditions of use studied. The risk of any cardiovascular event was lower in medium-frequency acetaminophen users compared with the reference group but only after adjustment for potential confounding variables. This result most likely reflects residual confounding.

In a previous study,[8] self-reported frequent (>22 d/mo) acetaminophen use was associated with a 35% relative increase in risk of experiencing a cardiovascular event (relative risk, 1.35; 95% CI, 1.14–1.59). This was of similar magnitude to that afforded by frequent NSAID use and the risk seemed highest in the most frequent users. Acetaminophen is among the most widely used drugs in the world and such an increased risk would be of huge public health importance and would be of greater absolute significance in higher risk patients. We found no association in higher risk patients although there was some overlap in the CIs around the risk estimate in our and the previous study. Studies have also shown an association between acetaminophen use and renal insufficiency and incident hypertension,[13] and a recent small randomized controlled clinical trial showed a small elevation in ambulatory blood pressure after a short period acetaminophen use in those with coronary artery disease.[7] This study failed to demonstrate other adverse effects on a variety of measures of hematologic, biochemical, and endothelial function but was underpowered for these end points, and a relationship

Table 3. HR (95% Confidence Intervals) for MI, Stroke, or Any Cardiovascular Event on Adjusted Analysis in the Whole Study Cohort

Covariates	MI	Stroke	Any Cardiovascular Event
Acetaminophen exposure	0.98 (0.76–1.27)	1.09 (0.86–1.38)	1.17 (0.99–1.34)
Age	1.01 (1.00–1.02)	1.04 (1.03–1.05)	1.02 (1.01–1.02)
Sex	0.55 (0.49–0.62)	0.85 (0.77–0.95)	0.66 (0.62–0.71)
Smoking	1.45 (1.25–1.63)	1.27 (1.09–1.47)	1.31 (1.19–1.45)
BMI	1.01 (0.99–1.03)	1.03 (1.00–1.03)	1.01 (1.00–1.02)
Diabetes mellitus	1.12 (0.99–1.28)	1.16 (1.03–1.31)	1.20 (1.11–1.30)
IHD	2.44 (2.160–2.76)	1.30 (1.15–1.48)	2.10 (1.94–2.27)
PVD	1.48 (1.10–2.00)	1.55 (1.14–2.11)	1.98 (1.63–2.40)
Stroke	1.51 (1.28–1.78)	3.39 (2.98–3.86)	2.27 (2.06–2.50)
Systolic BP	1.00 (1.00–1.00)	1.00 (0.99–1.00)	1.00 (1.00–1.01)
Diastolic BP	0.99 (0.99–1.00)	1.01 (1.00–1.02)	1.00 (0.99–1.00)
NSAID use	1.21 (1.03–1.43)	0.89 (0.75–1.06)	1.02 (0.98–1.22)
Aspirin use	0.76 (0.69–0.86)	0.86 (0.77–0.97)	0.89 (0.82–0.96)
Statin use	0.35 (0.30–0.42)	0.29 (0.24–0.35)	0.39 (0.35–0.44)

For acetaminophen exposure, the reference category is nonexposed patients. For sex, the reference category is male sex. For age, HR is per year increase in age. All above variables were included in the model.

BMI indicates body mass index; DBP, diastolic blood pressure; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PVD, peripheral vascular disease; and SBP, systolic blood pressure.

Table 4. HR (95% Confidence Intervals) for MI, Stroke, or Any Cardiovascular Event on Adjusted Analysis in the Propensity-Matched Sample (n=4000 per group)

Covariates	MI	Stroke	Any Cardiovascular Event
Acetaminophen exposure	0.67 (0.40–1.11)	1.31 (0.92–1.87)	1.16 (0.90–1.50)
Age	1.01 (0.99–1.02)	1.03 (1.02–1.05)	1.01 (0.99–1.02)
Sex	0.55 (0.46–0.67)	0.84 (0.71–1.02)	0.66 (0.58–0.74)
Smoking	1.58 (1.22–2.04)	1.18 (0.89–1.54)	1.24 (1.04–1.48)
BMI	1.01(0.98–1.03)	1.01 (0.99–1.04)	1.01 (0.99–1.03)
Diabetes mellitus	1.13 (0.92–1.39)	1.07 (0.87–1.31)	1.17 (1.03–1.34)
IHD	2.32 (1.89–2.84)	1.23 (0.99–1.52)	2.03 (1.78–2.31)
PVD	1.42 (0.83–2.44)	2.06 (1.26–3.35)	2.27 (1.65–3.12)
Stroke	1.54 (1.17–2.02)	3.23 (2.59–4.02)	2.10 (1.79–2.47)
Systolic BP	1.01 (1.00–1.01)	1.01 (1.01–1.02)	1.01 (1.01–1.01)
Diastolic BP	0.99 (0.98–1.01)	0.99 (0.98–1.00)	0.99 (0.98–0.99)
NSAID use	1.18 (0.92–1.53)	0.87 (0.70–1.14)	1.06 (0.89–1.26)
Aspirin use	0.77 (0.62–0.95)	0.90 (0.74–1.11)	0.91 (0.79–1.05)
Statin use	0.39 (0.29–0.49)	0.35 (0.26–0.46)	0.43 (0.34–0.51)

For acetaminophen exposure, the reference category is nonexposed patients. For sex, the reference category is male sex. For age, HR is per year increase in age. All above variables were included in the model.

BMI indicates body mass index; DBP, diastolic blood pressure; HR, hazard ratio; IHD, ischemic heart disease; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PVD, peripheral vascular disease; and SBP, systolic blood pressure.

between acetaminophen and increased cardiovascular risk is biologically plausible. Notably, we did not see a sustained increase in blood pressure in users of acetaminophen in a previous study using the CPRD so it is possible that acetaminophen does not increase the blood pressure in this population.[14] Acetaminophen acts through an indirect effect on the COX-2 enzyme[5,15] and perhaps on a central splice variant of this enzyme, COX-3.[6] Inhibition of COX-2, leading to reduced prostacyclin production and a prothrombotic state via unopposed action of thromboxane, may explain the increased risk of cardiovascular events associated with COX-2 selective inhibitor use. Recent data suggest that this may also occur after acetaminophen use.[16]

There are numerous differences between our study and the previous analysis from the Women's Health Study.[8] That study included only women, aged 30 to 55 years, from a particular professional group (nurses). Our study included both men and women and we only included patients with a diagnosis of hypertension aged >65 years. This makes our cohort higher risk and it is possible that the effects of acetaminophen are less important in higher risk patients who are receiving other medications, such as statins and antithrombotic drugs. We did not see a relationship when we looked only at women. Our study was based on data contained within the CPRD, a registry of routinely collected clinical data with accurate prescription data. The previous study was based on self-reported medication use. We also used a different approach to statistical analysis and while both studies used adjustment for potential confounders, we incorporated a propensity-matched analysis.

We performed a post hoc sample size calculation to statistical power. Based on the event rate in the nonexposed patients, a sample size of 2200/group would give 90% power (α=0.05) to detect a 15% relative increase in risk (17.0%–19.6%) in any cardiovascular event with acetaminophen exposure using a log-rank test. A sample size of 1946 per group would give 90% power (α=0.05) to detect a 15% relative increase in MI (7.38–8.50%) and a sample size of 3432 per group would give 90% power to detect a 11% relative increase in stroke (9.0%–10.0%). Our sample size was substantially larger than either of these permutations, so our study has sufficient power to exclude a clinically meaningful difference between exposure groups.

We took a number of steps to minimize potential for confounding and biases. We used a database with a high standard of diagnostic reporting.[11] The quality of data about the occurrence of myocardial infarction and stroke in the CPRD has been extensively validated; in the case of myocardial infarction, a previous study found that in excess of 90% of recorded cases could be verified objectively by electrocardiographic, blood, or clinical data[17] and similar validation has been undertaken for stroke.[18] We chose not to subdivide stroke events into ischemic or hemorrhagic as this distinction may be less accurate in primary care records and because a rise in blood pressure would increase risk of both subtypes. Our study population is entitled to free medicine prescriptions and had a chronic condition (hypertension) subject to surveillance in primary care. The observation that large numbers received an acetaminophen prescription during the study provides reassurance that acetaminophen exposure has not been underestimated. We were able to obtain details of and adjust for baseline variables, such as age, sex, traditional cardiovascular risk factors, and preventative drug treatments. We also performed a propensity-matched analysis to further reduce potential for confounding and groups were well matched after matching. These included variables, such as aspirin use and statin use, which were more prevalent in the acetaminophen exposed patients and could have biased the whole cohort analysis toward the null.

Limitations

There are several limitations to consider despite the steps taken above. In the United Kingdom, acetaminophen is available in numerous over the counter preparations. Because our control patients were never once prescribed acetaminophen and were eligible for free prescriptions, it is unlikely they purchased and consumed this drug. However, it is possible there was some acetaminophen use in the nonacetaminophen group and this could lead to underestimation of risk attributed to acetaminophen.

We know patients were prescribed acetaminophen. However, we cannot be certain that they took it. We attempted to account for these factors by only including patients who received ≥3 prescriptions, the assumption being that patients would only ask for repeated prescriptions if they had used the previous supply. Furthermore, we used acetaminophen exposure as a time-dependent variable, meaning patients

were only classed as exposed during the periods closest to a prescription date. In the CPRD, the daily dose is recorded in free text rather than in a structured fashion.[19] Typically, prescriptions are for 1 g of acetaminophen 4× per day or on an as required basis, so we cannot be certain of the dose of acetaminophen being used. In our study, only a small number met our definition of a high-frequency users, although the larger number of medium frequency users also received a large number of acetaminophen prescriptions. However, our study lacks power to explore definitely different amounts of acetaminophen exposure.

A key issue is the potential for confounding by indication. Acetaminophen use has been associated with higher than expected mortality from a variety of causes.[20] We are unable to identify the specific indication for each acetaminophen prescription. We excluded patients with renal impairment as such patients may be preferentially prescribed acetaminophen in preference to nonsteroidal antiinflammatory drugs but have high cardiovascular risk. We also excluded patients with asthma, chronic obstructive pulmonary disease, renal impairment, and rheumatoid arthritis for similar reasons. These exclusion criteria were applied at source and therefore the exact numbers are unknown. These criteria also raise the possibility of selection bias. The CPRD includes data on ≈5 million participants but because of inclusion of only patients aged >65 years with hypertension, who did not have the above conditions, we included only 24 496 patients in our analysis. Thus, our findings cannot be extrapolated to other risk groups, people without hypertension or younger people and particularly women with lower cardiovascular risk, where an association has previously been demonstrated.

Despite using propensity matching, it is possible that residual confounding exists. Further, even where we adjusted for potential confounding variables, we cannot be certain that data were not missing and that they were accurately recorded for all participants.

Perspectives

We have found that patients prescribed regular acetaminophen were not at higher risk of stroke or myocardial infarction compared with those to whom acetaminophen had not been prescribed. To definitively establish whether acetaminophen use increases cardiovascular risk, and at what dose and frequency, randomized clinical trials would be needed. These are unlikely to be conducted and would be difficult to justify if the premise of the trial is to demonstrate harm. Our data at least provide reassurance that regular users of acetaminophen who are being actively managed for hypertension do not seem to be at increased risk of vascular events when potential confounding factors are taken into consideration. Further epidemiological studies should be performed in different risk groups to inform future guidance about the use of acetaminophen in high-risk patients.

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J. Dawson and G.T. McInnes designed the study. J.Dawson wrote the article. R. Morton performed data extraction. R.L. Fulton performed statistical analysis. A.F. Dominiczak, R.M. Touyz, P.A. Meredith, D.S. Morrison, M.R. Walters, and S. Padmanabhan participated in study management and critically appraised the article.

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Disclosures

None.

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Novelty and Significance

What Is New?

- This is the first study examining the association between acetaminophen use and cardiovascular events in patients with hypertension. It is also the first epidemiological study of acetaminophen use using prescription data rather than self-reported data.

What Is Relevant?

- There is increasing debate about the cardiovascular safety of acetaminophen and clinical trials of this topic are unlikely to be conducted so epidemiological analyses of prescription data in different cohorts will be needed.

Summary

In this observational study, the use of acetaminophen was not associated with an increased risk of myocardial infarction or stroke in a large cohort of hypertensive patients.