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ORIGINAL RESEARCH

Excess Mortality in Aspirin and Dipyrone (Metamizole) Co-Medicated in Patients With Cardiovascular Disease: A Nationwide Study

Amin Polzin, MD*; Lisa Dannenberg, MD*; Carolin Helten, MD; Martin Pöhl, MD; Daniel Metzen; Philipp Mourikis, MD; Christof Dücker, MD; Ursula Marschall, MD; Helmut L'Hoest, MD; Beata Hennig; Saif Zako, MD; Kajetan Trojovsky; Tobias Petzold, MD; Christian Jung, MD; Bodo Levkau, MD; Tobias Zeus, MD; Karsten Schrör, MD; Thomas Hohlfeld, MD†; Malte Kelm, MD†

BACKGROUND: Pain is a major issue in our aging society. Dipyrone (metamizole) is one of the most frequently used analgesics. Additionally, it has been shown to impair pharmacodynamic response to aspirin as measured by platelet function tests. However, it is not known how this laboratory effect translates to clinical outcome.

METHODS AND RESULTS: We conducted a nationwide analysis of a health insurance database in Germany comprising 9.2 million patients. All patients with a cardiovascular event in 2014 and subsequent secondary prevention with aspirin were followed up for 36 months. Inverse probability of treatment weighting analysis was conducted to investigate the rate of mortality, myocardial infarction, and stroke/transient ischemic attack between patients on aspirin-dipyrone co-medication compared with aspirin-alone medication. Permanent aspirin-alone medication was given to 26,200 patients, and 5946 patients received aspirin–dipyrone co-medication. In the inverse probability of treatment weighted sample, excess mortality in aspirin–dipyrone co-medicated patients was observed (15.6% in aspirin-only group versus 24.4% in the co-medicated group, hazard ratio [HR], 1.66 [95% CI, 1.56–1.76], $P<0.0001$). Myocardial infarction and stroke/transient ischemic attack were increased as well (myocardial infarction: 1370 [5.2%] versus 355 [5.9%] in aspirin-only and co-medicated groups, respectively; HR, 1.18 [95% CI, 1.05–1.32]; $P=0.0066$, relative risk [RR], 1.14; number needed to harm, 140. Stroke/transient ischemic attack, 1901 [7.3%] versus 506 [8.5%] in aspirin-only and co-medicated groups, respectively; HR, 1.22 [95% CI, 1.11–1.35]; $P<0.0001$, RR, 1.17, number needed to harm, 82).

CONCLUSIONS: In this observational, nationwide analysis, aspirin and dipyrone co-medication was associated with excess mortality. This was in part driven by ischemic events (myocardial infarction and stroke), which occurred more frequently in co-medicated patients as well. Hence, dipyrone should be used with caution in aspirin-treated patients for secondary prevention.

Key Words: aggregation ■ aspirin ■ co-medication ■ dipyrone ■ platelet activation ■ platelet inhibition

More than 30% of adults experience chronic pain.[1] The pyrazolone derivate dipyrone (metamizole, novamidazophen, novaminsulfon, sulpyrine, and methylaminoantipyrine methanesulfonate) is a potent analgesic and antipyretic.[2] Because of its rare but severe side effect of agranulocytosis, it was withdrawn in the United States and parts of Europe.[3] However, sufficient alternatives are rare.[4] In accordance, defined

Correspondence to: Amin Polzin, MD, Moorenstraße 5, Klinik für Kardiologie, Pneumologie und Angiologie, Heinrich Heine University Medical Center Düsseldorf, 40225 Düsseldorf, Germany. E-mail: amin.polzin@med.uni-duesseldorf.de

*A. Polzin and L. Dannenberg contributed equally as co-first authors.

†T. Hohlfeld and M. Kelm contributed equally as co-last authors.

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CLINICAL PERSPECTIVE

What Is New?

- Our study revealed that dipyrone-impaired pharmacodynamic response to aspirin, measured by platelet function tests, translates to increased major adverse cardiac and cerebrovascular events.

What Are the Clinical Implications?

- This finding is not only a laboratory phenomenon but has clinical implications.
- Dipyrone and aspirin co-medication should not be given simultaneously.

Nonstandard Abbreviations and Acronyms

IPTW	inverse probability of treatment weighted
MACCE	major adverse cardiac and cerebrovascular events

daily doses quadrupled over the last 15 years in parts of Europe.[5,6] In some countries, dipyrone is even the most frequently used analgesic.[7] Moreover, it is available without prescription as over-the-counter medication in several countries.[8] Besides agranulocytosis, other side effects were described.[3] It was shown that dipyrone attenuates pharmacodynamic response to aspirin. Dipyrone hinders access of aspirin to the active center of cyclooxygenase (COX)-1.[9,10] Therefore, in this nationwide study, we aimed to investigate whether this impaired laboratory response to aspirin translates to clinical outcome.

METHODS

Data, analytic methods, and study materials will not be available on request because of patient privacy regulations.

Design, Population, and Follow-Up

We conducted a retrospective, observational, nationwide study between 2014 and 2017. The study conformed to the Declaration of Helsinki and was approved by the University of Düsseldorf Ethics Committee (vote no 2018-22). The general health insurance company BARMER (Wuppertal, Germany) registry contains patient data of all insured patients. Inclusion criteria were (1) cardiovascular event (acute coronary syndrome with and without percutaneous transluminal stent placement or bypass grafting, stroke or transient ischemic attack [TIA], percutaneous transluminal angioplasty because of peripheral artery disease) in 2014 and (2) documented permanent aspirin medication (75–100 mg od) throughout follow-up. Only uninterrupted prescription of dipyrone was documented and included. Time-Zero was defined by date of index event. The index date identification period was January 2014 until December 2014. The BARMER database registered the index event and index date by coded hospital stay including *International Statistical Classification of Diseases and Related Health Problems* (*ICD-10*) coded diagnosis. Each patient was followed from the start of follow-up for 36 months or until death or loss to follow-up, whichever occurred first. There was no omitted time period in this analysis (Table 1).

Comorbidities and co-medication were collected via *ICD-10*, International Classification of Procedures in Medicine, and Acute Toxic Class coded in the electronic BARMER database. Comorbidities were assessed at time of index event. Obesity was classified as body mass index >30 kg/m^2. Chronic kidney disease was classified as kidney function that is estimated glomerular filtration rate <60 mL/min.

Outcomes

Myocardial infarction (MI) and stroke were highlighted as major outcomes because they define 85% of the causes of cardiovascular death.[11] Cardiovascular events are the most severe and meaningful complications of high on-treatment platelet reactivity, (ie, impaired pharmacodynamic response to aspirin under dipyrone comedication).

Outcomes were coded by *ICD-10* and International Classification of Procedures in Medicine. Death included all causes for mortality. Major adverse cardiac and cerebrovascular events (MACCE) comprised death, MI, and stroke/TIA. MI summed ST-segment–elevation MI (I21.0-3) and non–ST-segment–elevation MI (I21.4). Stroke/TIA consisted of ischemic stroke (I63), intracranial bleeding (I61), stroke without definition of bleeding or ischemia (I64), and TIA or associated symptoms based on clinical presentation (G45) coded by *ICD-10*.

Statistical Analysis

SPSS (IBM, New York, USA) and R (version 3.6.1, The R Foundation) were used for statistical analyses. To determine differences in patient characteristics between groups, the *t* test and absolute standardized differences[12] were used to compare continuous variables. Fisher exact test and absolute standardized differences were used to compare categorical variables.

To explore differences in risk for all-cause mortality, MI, and stroke/TIA, we conducted an inverse

Table 1. Temporal Anchors

Term	Definition
Base anchor	
Data extraction date	November 2018
Source data range	January 1, 2014–December 31, 2014
Study period	January 1, 2014–December 31, 2017
First-order anchors	
Cohort entry date	Date of index event (cardiovascular event) during hospital stay in 2014
Outcome event date	Outcome event occurrence in 36 mo from 2014 to 2017
Second-order anchors	
Washout window for exposure	January 1, 2014–December 31, 2017 Both new and prevalent exposure to aspirin and dipyrone were included
Washout window for outcome	January 1, 2014–December 31, 2017 Incident outcomes were assessed over 36 mo of follow-up
Exclusion assessment window	Assessment at time point of index event: if exclusion criteria applied, no inclusion despite suitable cardiovascular event
Covariate assessment window	Covariates assessed during year of index event, January–December 2014
Exposure assessment window	January 1, 2014–December 31, 2017
Follow-up window	January 1, 2014–December 31, 2017: 36-mo follow-up, or earlier until death or loss to follow-up, whichever occurred first. There was no omitted time period in this analysis

probability of treatment weighted (IPTW) Cox regression to rule out confounding caused by differences in patients' characteristics between groups.[12,13] To conduct IPTW, the propensity score was computed via logistic regression. All patient characteristics (Table 2) were used to predict the propensity score, without respect to whether they were different or not. We included all variables because it is known that even small differences may bias the results. Thereby, we avoided possible misbalancing because of the weighting process regarding equal parameters. The patients' inverse probability to receive treatment was computed as stabilized weights[14] with the quotient of marginal probability to receive aspirin dipyrone treatment/propensity score for the aspirin–dipyrone group and the quotient of (1–marginal probability to receive aspirin dipyrone treatment)/(1–propensity score for the aspirin-alone group). The marginal probability[14] to receive aspirin–dipyrone treatment was computed with the quotient of (number of patients in aspirin+dipyrone group)/(total number of patients). The use of stabilized weights in IPTW is recommended to reduce variability in the inverse probability of treatment-weighted models.[14] Furthermore, stabilized weights do not lead to an inflation of sample size and an increase in type 1 error rate, as is the case when nonstabilized weights are used.[15] Next, an inverse probability of treatment-weighted sample was constructed. To ensure balance in patient characteristics between groups, we compared patient characteristics before and after IPTW. An absolute standardized differences of <10% after IPTW was considered well balanced[12,16] (Table 2). Hazard ratios (HR) with 95% CI were computed via Cox regression weighted by the stabilized inverse probability of treatment (Table 3). Furthermore, we computed relative risk (RR), absolute risk increase, and the number needed to harm (NNH) for the IPT weighted sample and the unweighted sample. To explore the robustness of our results, HR with 95% CI were computed via multivariate Cox regression. All patient characteristics (Table 2) were included as covariates into the multivariate Cox model. Inverse probability of treatment weighted Kaplan–Meier cumulative events curves with log rank test were used to visualize results.

RESULTS

Patients

The registry contained a total of 9.2 million patients. Some patients (32 146) had a cardiovascular event in 2014 with consecutive permanent aspirin medication. Of these, 26 200 patients had permanent aspirin-alone treatment and 5946 patients had additional permanent dipyrone co-medication (Figure 1). Mean dipyrone dose was 2.06 g per day.

Aspirin-alone treated patients were 70±12 and aspirin–dipyrone patients 74±12 years of age (P<0.001); 58.5% versus 47.0% were male (P<0.001). Patients in the aspirin–dipyrone group more often showed chronic kidney disease (15.2% versus 23.0%, P<0.001), heart failure (17.2% versus 20.3%, P<0.001), type 2 diabetes (27.0% versus 31.5%, P<0.001), atrial fibrillation (12.5% versus 19.2%, P<0.05), prior MI (4.1% versus 5.0%, P<0.01), and malignant neoplasia (1.4% versus 3.2%, P<0.001) than patients in the aspirin-alone group. Pre-existing coronary artery disease was higher in the aspirin-alone group than in the aspirin–dipyrone group

Table 2. Characteristics of All Included Patients Before and After IPTW Analysis

Characteristic before IPTW	Aspirin-alone (n=26 200)	Aspirin–dipyrone (n=5946)	ASD* (%)
Age, y, mean±SD†	70±12	74±12	33.35
Male sex, no. (%)†	15 333 (58.5)	2794 (47.0)	23.19
Obesity, no. (%)	2155 (8.2)	524 (8.8)	2.15
CKD, no. (%)†	3974 (15.2)	1368 (23.0)	19.94
Arterial hypertension, no. (%)	17 760 (67.8)	4007 (67.4)	0.85
Hypertensive heart disease, no. (%)	3233 (12.3)	747 (12.6)	0.91
Heart failure, no. (%)†	4508 (17.2)	1207 (20.3)	7.95
Diabetes type 2, no. (%)†	7070 (27.0)	1871 (31.5)	9.90
Diabetes type 1, no. (%)	147 (0.6)	46 (0.8)	2.40
Prior myocardial infarction, no. (%)†	1075 (4.1)	296 (5.0)	4.32
Pre-existing CAD, no. (%)†	13 026 (49.7)	2586 (43.5)	12.45
Prior stroke/TIA	875 (3.3)	210 (3.5)	1.10
Prior intracranial bleeding, no. (%)	80 (0.3)	21 (0.4)	1.69
Malignant neoplasia, no. (%)†	368 (1.4)	189 (3.2)	12.03
Insurance cancellation during follow-up†	446 (1.7)	57 (1.0)	6.07
Atrial fibrillation, no. (%)†	3273 (12.5)	1143 (19.2)	18.42
Co-medication, no. (%)			
ACE inhibitor	1673 (6.4)	352 (5.9)	2.08
β-Blocker	16 665 (63.6)	3744 (63.0)	1.24
Calcium channel antagonist	339 (1.3)	76 (1.3)	0
Clopidogrel†	555 (2.1)	91 (1.5)	4.51
Statin†	20 895 (79.8)	4074 (68.5)	26.03
Spironolactone†	1740 (6.6)	527 (8.9)	8.61
Characteristic after IPTW	**Aspirin-alone (n=26 197)‡**	**Aspirin–dipyrone (n=5973)‡**	**ASD* (%)**
Age, y, mean±SD†	71±12	70±13	4.21
Male sex, no. (%)	14 771 (56.4)	3386 (56.7)	0.61
Obesity, no. (%)	2190 (8.4)	515 (8.6)	0.72
CKD, no. (%)	4359 (16.6)	995 (16.7)	0.27
Arterial hypertension, no. (%)	17 739 (67.7)	4040 (67.6)	0.21
Hypertensive heart disease, no. (%)	3246 (12.4)	734 (12.3)	0.30
Heart failure§, no. (%)	4660 (17.8)	1077 (18.0)	0.52
Diabetes type 2, no. (%)	7296 (27.9)	1684 (28.2)	0.67
Diabetes type 1, no. (%)	157 (0.6)	36 (0.6)	0
Prior myocardial infarction, no. (%)	1120 (4.3)	260 (4.4)	0.49
Pre-existing CAD, no. (%)	12 737 (48.6)	2978 (49.8)	2.40
Prior stroke/TIA	882 (3.4%)	192 (3.2%)	1.12
Prior intracranial bleeding, no. (%)	83 (0.3)	20 (0.3)	0
Malignant neoplasia, no. (%)	462 (1.8)	110 (1.8)	0
Insurance cancellation during follow-up	426 (1.6%)	78 (1.3%)	2.51
Atrial fibrillation, no. (%)†	3420 (13.1)	965 (16.2)	8.78
Co-medication, no. (%)			
ACE inhibitor	1652 (6.3)	379 (6.3)	0
β-Blocker	16 649 (63.6)	3857 (64.6)	2.08
Calcium channel antagonist	338 (1.3)	77 (1.3)	0
Clopidogrel†	570 (2.2)	85 (1.4)	6.02
Statin	20 353 (77.7)	4664 (78.1)	0.96
Spironolactone	1849 (7.1)	432 (7.2)	0.39

Obesity refers to body mass index >30 kg/m^2. ACE indicates angiotensin-converting enzyme; ASD, absolute standardized difference; CAD, coronary artery disease; CKD, chronic kidney disease (glomerular filtration rate <60 mL/min); IPTW, inverse probability of treatment weighting; and TIA, transient ischemic attack.

*Absolute standardized difference.

†P<0.05 for the between-group comparison.

‡Numbers of patients in each group differ from whole cohort because of IPTW.

§Heart failure was defined as reduced left ventricular ejection function <45%.

Table 3. Study End Points of IPTW Cox Regression and Multivariate Cox Regression Analyses

IPTW Cox regression	Aspirin-alone (n=26 197)*	Aspirin–dipyrone (n=5973)*	HR (95% CI)	*P* value†	RR	ARI	NNH
All-cause mortality	4089 (15.6%)	1455 (24.4%)	1.66 (1.56–1.76)	<0.001	1.56	8.75%	11
MACCE	6522 (24.9%)	2023 (33.9%)	1.45 (1.38–1.53)	<0.001	1.36	8.97%	11.15
MI	1370 (5.2%)	355 (5.9%)	1.18 (1.05–1.32)	0.0066	1.14	0.71%	140
Stroke/TIA	1901 (7.3%)	506 (8.5%)	1.22 (1.11–1.35)	<0.001	1.17	1.21%	82
Bleeding	117 (0.4%)	34 (0.6%)	1.33 (0.91–1.95)	0.142	1.27	0.12%	816
Multivariate Cox regression	**Aspirin-alone (n=26 200)**	**Aspirin–dipyrone (n=5946)**	**HR (95% CI)**	***P* value†**	**RR**	**ARI**	**NNH**
All-cause mortality	3784 (14.4%)	1889 (31.8%)	1.72 (1.62–1.82)	<0.001	2.20	17.33%	6
MACCE	6252 (23.9%)	2397 (40.3%)	1.52 (1.45–1.60)	<0.001	1.69	16.45%	6.08
MI	1374 (5.2%)	332 (5.6%)	1.14 (1.01–1.29)	0.0344	1.06	0.34%	295
Stroke/TIA	1889 (7.2%)	526 (8.8%)	1.28 (1.16–1.41)	<0.0001	1.23	1.64%	61
Bleeding	114 (0.4%)	39 (0.7%)	1.35 (0.93–1.97)	0.114	1.51	0.22%	453

MACCE was defined as mortality, stroke, or myocardial infarction. ARI indicates absolute risk increase; HR, hazard ratio of univariate Cox regression; IPTW, inversed probability of treatment weighting; MACCE, major adverse cardiac and cerebrovascular events; MI, myocardial infarction; NNH, number needed to harm; RR, relative risk; and TIA, transient ischemic attack.

*Numbers of patients in each group differ from whole cohort because of IPTW.

†*P* value of univariate Cox regression.

(49.7% versus 43.5%, *P*<0.001) Co-medication did not differ between groups apart from statin (79.8% versus 68.5%, *P*<0.001), spironolactone (6.6% versus 8.9%, *P*<0.001), and clopidogrel (2.1% versus 1.5%, *P*<0.05).

IPTW allocated 26 197 patient counts in the aspirin-alone and 5973 patient counts in the aspirin–dipyrone group. After IPTW, patients were well balanced based on absolute standardized differences. Patients in the aspirin-alone group were 71±12 and patients in the aspirin–dipyrone group were 70±13 years of age (*P*<0.05). There were 56.4% versus 56.7% who were male and 8.4% versus 8.6% were obese. Also, 16.6% versus 16.7% had chronic kidney disease, 67.7% versus 67.6% had arterial hypertension, 17.8% versus 18.0% had heart failure, 27.9% versus 28.2% had type 2 diabetes, and 13.1% versus 16.2% had atrial fibrillation. Prior MI occurred in 4.3% versus 4.4%, pre-existing coronary artery disease in 48.6% versus 49.8%, and malignant neoplasia in 1.8% in each group. There were 77.7% versus 78.1% on statin, 7.1% versus 7.2% on spironolactone, and 2.2% versus 1.4% on clopidogrel medication. Table 2 summarizes clinical and demographic characteristics of the patients before and after IPTW.

Outcomes

During follow-up, MACCE occurred in 8649 patients (26.9%) and 5673 (17.6%) patients died. Regarding nonfatal events, 1706 (5.3%) patients had a MI and 2415 (7.5%) patients had a stroke/TIA.

IPTW analysis revealed MACCE were higher in aspirin–dipyrone co-medicated patients, compared with aspirin-alone treated patients (6522 [24.9%] versus 2023 [33.9%]; HR, 1.45 [95% CI, 1.38–1.53]; *P*<0.001, RR, 1.36; NNH, 11.15, Table 3, Figure 2). The mortality was higher in patients taking aspirin–dipyrone (4089 [15.6%] versus 1455 [24.4%]; HR, 1.66 [95% CI, 1.56–1.76], *P*<0.0001, RR, 1.56; NNH, 11; Table 3, Figure 3). MI and stroke/TIA were increased as well (MI, 1370 [5.2%] versus 355 [5.9%]; HR, 1.18 [95% CI, 1.05–1.32]; *P*=0.0066, RR, 1.14, NNH, 140; Table 3, Figure 4A. Stroke/TIA, 1901 [7.3%] versus 506 [8.5%]; HR, 1.22 [95% CI, 1.11–1.35]; *P*<0.0001, RR, 1.17, NNH 82; Table 3, Figure 4B). Bleedings did not differ between the 2 groups (117 [0.4%] versus 34 [0.6%], HR, 1.33 [95% CI, 0.91–1.95]; *P*=0.142, RR, 1.27, NNH, 816).

Findings remained robust in multivariate Cox regression in the unweighted sample. MACCE occurred more often in the aspirin–dipyrone group (6252 [23.9%] versus 2397 [40.3%], HR, 1.52 [95% CI, 1.45–1.60]; *P*<0.001, RR, 1.69, NNH, 6.08). Mortality was more frequent in the aspirin–dipyrone group (3784 [14.4%] versus 1889 [31.8%], HR, 1.72 [95% CI, 1.62–1.82], *P*<0.0001, RR, 2.2, NNH, 6). MI and stroke/TIA were higher in the aspirin–dipyrone group as well (MI, 1375 [5.2%] versus 332 [5.6%], HR, 1.14 [95% CI, 1.01–1.29], *P*=0.0344, RR, 1.06, NNH, 294.72; Stroke/TIA 1889 [7.2%] versus 526 [8.8%], HR, 1.28 [95% CI, 1.16–1.41], *P*<0.0001, RR, 1.23, NNH, 61; Table 3). Again, bleedings did not differ between the groups (114 [0.4%] versus 39 [0.7%]; HR, 1.35 [95% CI, 0.93–1.97; *P*=0.114, RR 1.51, NNH, 453).

DISCUSSION

The major findings of this nationwide analysis were (1) that aspirin and dipyrone co-medication is associated with excess all-cause mortality, and (2) that this was in part driven by ischemic events (MI and stroke), which were more frequent in co-medicated patients as well.

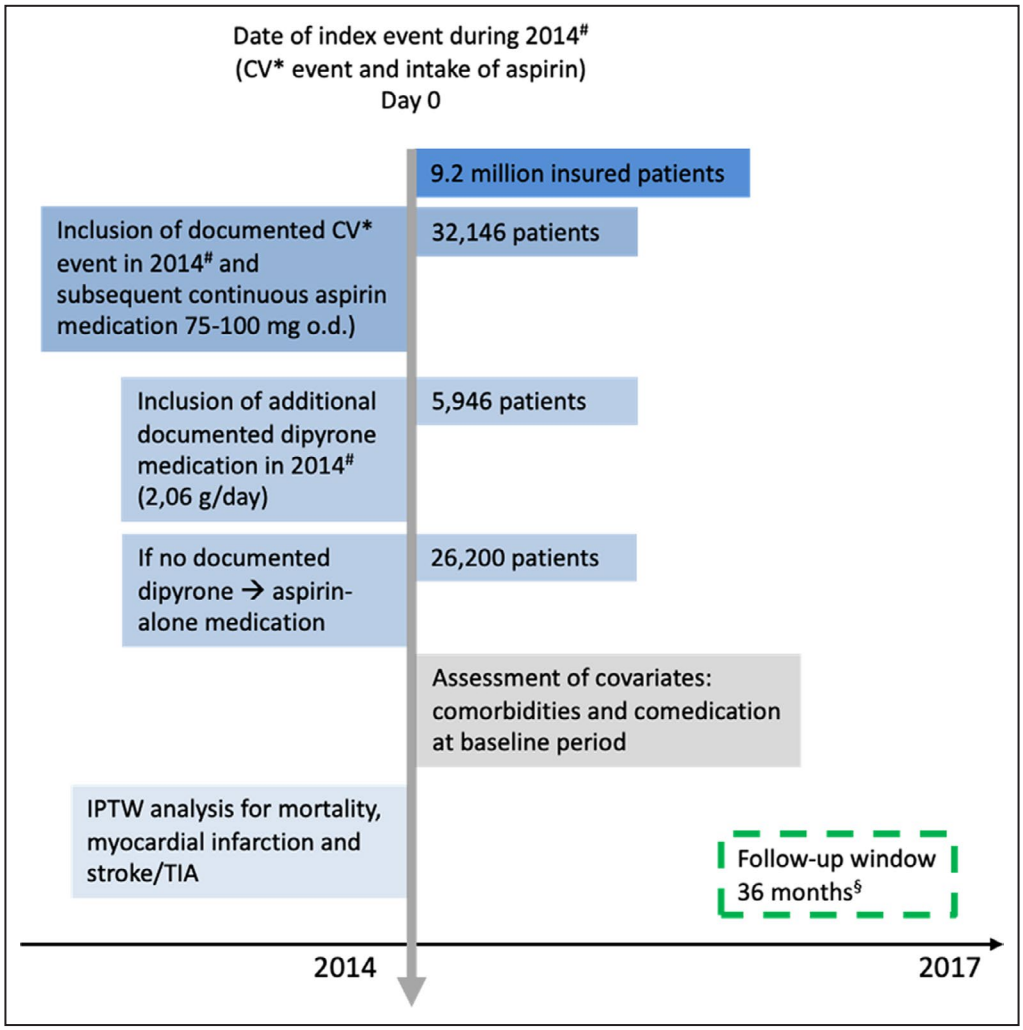

Figure 1. Flow chart.
*CV-event, cardiovascular event (acute coronary syndrome with and without percutaneous transluminal stent placement or bypass grafting, stroke or transient ischemic attack [TIA], percutaneous transluminal angioplasty because of peripheral artery disease). #January 1, 2014 to December 31, 2014. §Follow-up 36 months from 2014 until 2017. Censor: Death or loss to follow-up, whichever occurred first. No omitted time period. IPTW indicates inverse probability of treatment weighting; and o.d., once daily.

Aspirin is crucial in secondary prevention in patients with acute coronary syndrome and chronic coronary syndrome. Its role in primary prevention of high-risk patients is still under discussion.[17–20] However, pharmacodynamic response varies interindividually because of comorbidities,[21,22] gene alterations, noncompliance, or drug–drug interactions.[9] Aspirin exerts its antiplatelet effects by irreversible acetylation of serine 530 near the active site of COX-1. This leads to platelet inhibition during the life span of the platelet.[23] Dipyrone operates its analgesic effects by reversible hydrogen bonds with serine 530 and tyrosin 385 in the COX.[10,24] Aspirin plasma half-life is ≈20 minutes.[25] Dipyrone plasma half-life is substantially longer (>2 hours). Hence, dipyrone may hinder aspirin access to COX[26] when (short-lived) aspirin is administered during the (longer) time interval where dipyrone is present at pharmacologically active concentrations in plasma. This direct drug–drug interaction at the level of COX-1 frequently causes impaired aspirin antiplatelet effects.[10] In a previous study, we showed that the order of medication intake is crucial: ingestion of aspirin 30 minutes before metamizole prevents high on-treatment platelet reactivity to aspirin. Additionally, oral intake and lowest possible doses are favorable, because they reduce the occurrence of high on-treatment platelet reactivity.[27]

In this nationwide analysis, we were now able to observe that this previously shown impaired pharmacodynamic response translates to clinical outcome. In particular, mortality was substantially higher in co-medicated patients. Risk of nonfatal MI and stroke were significantly higher in co-medicated patients as

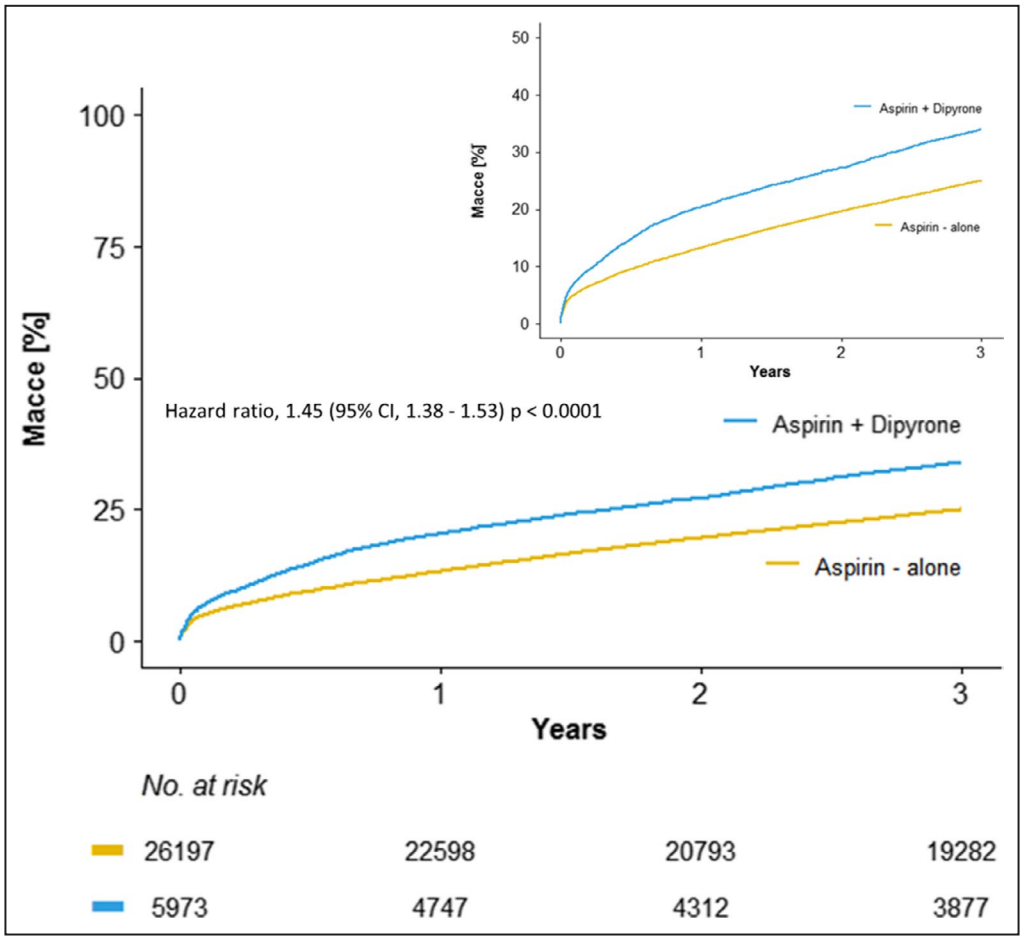

Figure 2. Kaplan–Meier curves of IPTW analysis with hazard ratios of IPTW Cox regression analysis for MACCE (log-rank test: *P*<0.0001, 95% CI, 1.38–1.53).
The inset figure is a magnification of the larger figure to show a better distinction between the 2 graphs. IPTW indicates inverse probability of treatment weighting; and MACCE, major adverse cardiac and cerebrovascular events.

well. Surprisingly, co-medicated patients had "only" a 14% increased risk for acute nonfatal MI, whereas risk of death was 72% higher in aspirin–dipyrone-treated patients. Rate of neoplasia was very low in this study (<4%). Hence, it seems reasonable that mortality was driven by cardiovascular events, because this is the most common cause of death in Western countries.[28]

However, the excess mortality in co-medicated patients might not be attributable to inhibition of aspirin antiplatelet effects alone. The ATT (Antithrombotic Trialists' Collaboration) revealed a 33% risk reduction of mortality by aspirin.[29] A more contemporary meta-analysis by the ATT showed a reduction of mortality by "only" 13%.[30] The latter compared antiplatelet therapy versus control and different antiplatelet regimens, but not aspirin in particular. We could not compare our data to a control group, because we did not include a group without aspirin medication, but we attributed the reduction in mortality risk to the protective effect of aspirin-alone versus the inhibitory effect of co-medication dipyrone. Another reason for this excess mortality in co-medicated patients could be adverse dipyrone effects beyond impairing pharmacodynamic response to aspirin (eg, agranulocytosis, severe dermal reactions, inhibition of steroidogenesis, and gastrointestinal and renal toxicity have enhanced mortality).[2,31–33] In a randomized-controlled trial we would expect the groups not to differ significantly. In our study, we can only guarantee this for those variables we controlled for. Additionally, in this observational study, it was not possible to control for pain itself. Pain might be associated with mortality independently of aspirin–dipyrone co-medication.[34] However, a possible association between pain and mortality is controversial.[34] Additionally, it is not known whether this association could even be reversed by optimal management of pain. Currently, some studies reported an association between chronic pain and mortality,[35–37] but others did not.[38–40] A meta-analysis suggested that this association was true in cancer pain.[41] In the

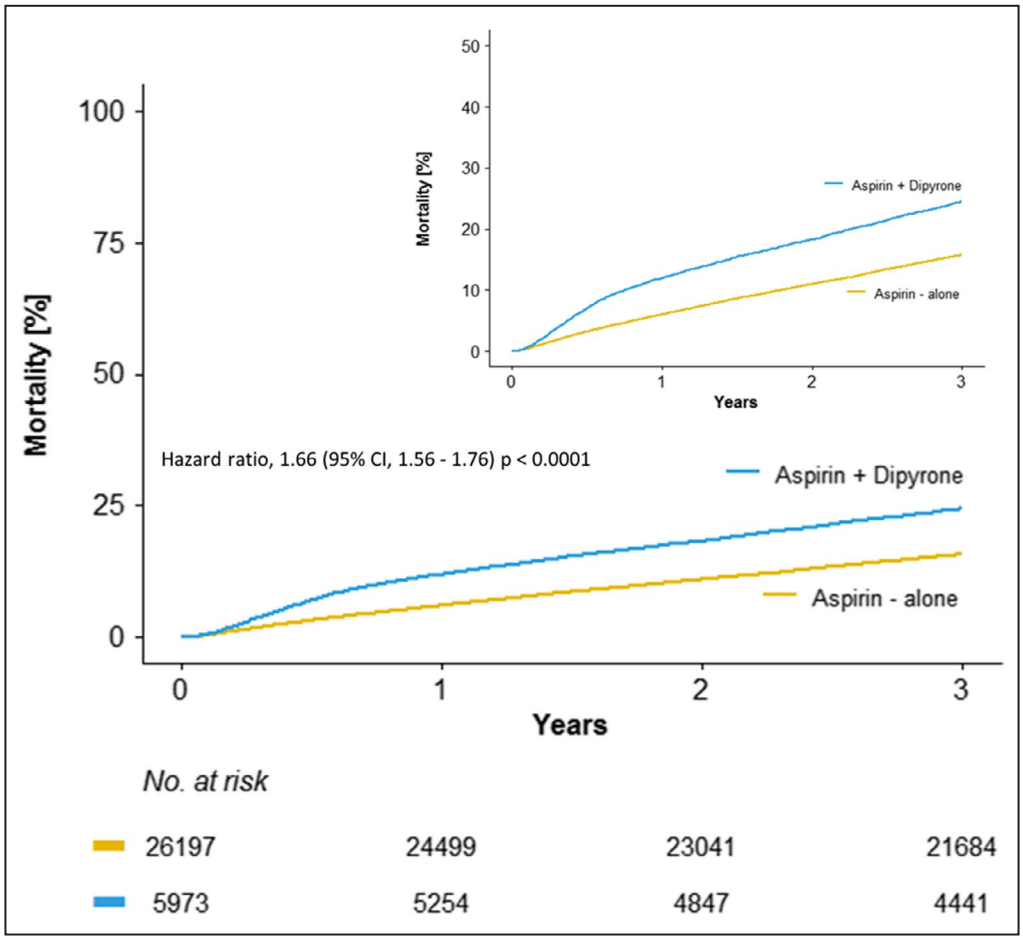

Figure 3. Kaplan–Meier curves of IPTW analysis with hazard ratios of IPTW Cox regression analysis for all-cause mortality (log-rank test: *P*<0.0001, 95% CI, 1.56–1.76).
The inset figure is a magnification of the larger figure to show a better distinction between the 2 graphs. IPTW indicates inverse probability of treatment weighting.

present study, patients were matched for neoplasia to minimize this bias. Therefore, excess of mortality might not be explained by (cancer) pain itself.

Many physicians consider dipyrone as indispensable because of the lack of alternatives. It works very effectively with tumor, chronic, or colicky pain, and has a spasmolytic component, where other nonsteroidal anti-inflammatory drugs are less potent. It helps reducing the use of opioid drugs. Furthermore, if patients present with intolerances or allergies, metamizole can be an effective alternative. German data reports show that prescriptions for metamizole doubled over the last 10 years, and are 15 times higher than 1986, when the substance became available only via medical prescription.[42] Metamizole, though banned in some countries, is still widely used and available over the counter or on a prescription basis in several countries worldwide.[43] This indicates that the demand for dipyrone remains very high. This is emphasized by the fact that extensive dipyrone use is even reported in countries such as the United States where dipyrone is prohibited.[8]

Many nonsteroidal anti-inflammatory drugs have the potential to interact with the antiplatelet action of aspirin. Some may even displace aspirin from the salicylate-binding site because of their substantially higher lipophilicity.[26] Ibuprofen was shown to interact with aspirin in a dose-dependent manner.[44] Interestingly, diclofenac did not affect aspirin antiplatelet effects, which is in line with its decreased affinity to COX-1.[44] With the view to the interaction on the level of the COX-1, use of selective COX-2 inhibitors (eg, rofecoxib and celecoxib) might be reasonable in aspirin-treated patients. A recent study from patients with osteoarthritis and celecoxib medication revealed that there was indeed no relevant reduction of aspirin antiplatelet effects.[45] However, several studies reported interference with aspirin as well. This was attributed to partial binding of celecoxib to a subunit of COX-1.[46] In accordance, use of COX-2 inhibitors was also shown to be associated with enhanced risk of ischemic events.[47] In general, nonsteroidal anti-inflammatory drugs were demonstrated to be associated with a higher incidence

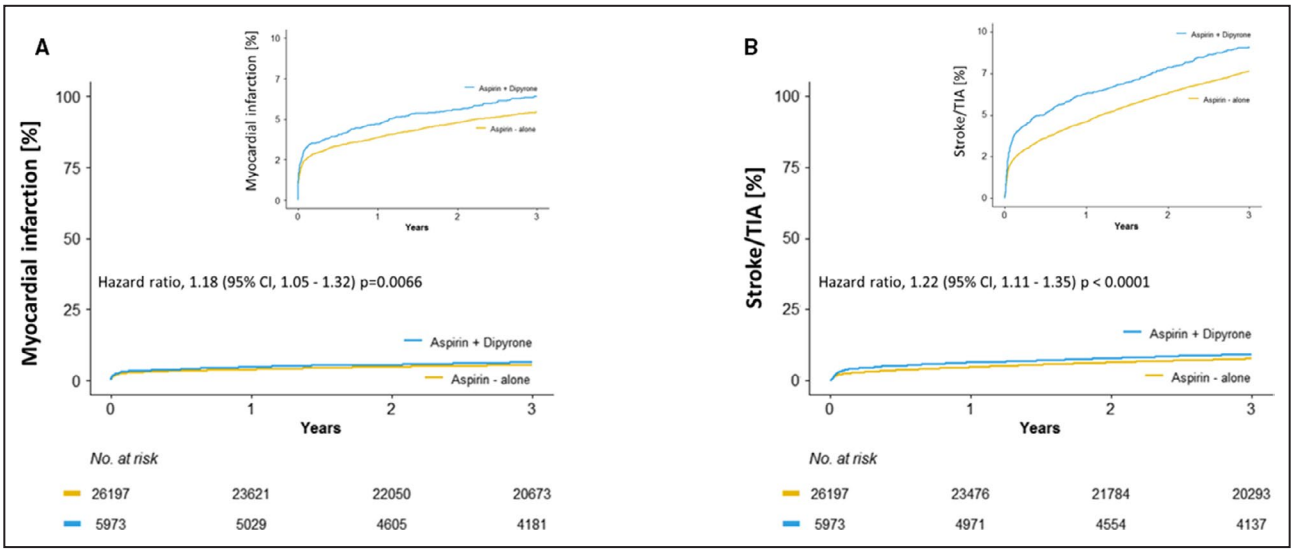

Figure 4. Kaplan–Meier curves of IPTW analysis with hazard ratios of IPTW Cox regression analysis for (A) myocardial infarction (log-rank test: *P*=0.0066, 95% CI, 1.05–1.32) and (B) for stroke/TIA (log-rank test: *P*<0.0001, 95% CI, 1.11–1.35). The inset figure is a magnification of the larger figure to show a better distinction between the 2 graphs. IPTW indicates inverse probability of treatment weighting; and TIA, transient ischemic attack.

of MACCE.[48–51] Acetaminophen, another nonopioid analgesic, has only limited analgesic potency, is liver toxic, and may increase the risk of coronary artery disease.[52] Opioids are only recommended as second-line analgesics based on the recommendations of the World Health Organization.[53] Especially since the "opioid crisis," their side effects were kept in mind. These factors contributed to increasing dipyrone use worldwide. However, this study revealed an excess mortality in aspirin–dipyrone co-medicated patients. Hence, alternative antithrombotic[54] or pain management strategies are urgently needed. We could show that factor Xa inhibition has direct antiplatelet effects: Factor Xa is a potent platelet agonist that induces platelet activation, mediated by protease-activated receptor 1. By inhibiting this pathway, rivaroxaban directly acts as an antiplatelet drug.[55] In the Cardiovascular Outcomes for People Using Anticoagulation Strategies trial, factor Xa inhibition alone reduced cardiovascular events, though it was not superior to aspirin.[56] Therefore, at the moment aspirin remains an important mainstay in antiplatelet therapy.

This study has several limitations. It was a cohort study, not a prospective randomized placebo-controlled trial. Patient characteristics differed between cohorts. IPTW was applied to account for differences in baseline characteristics, medical history, and others. However, this technique cannot control for unmeasured confounders. On the contrary, this design offered the opportunity to investigate a large, nationwide cohort of patients. It represents an all-comers design reflecting real-world data. Furthermore, this study was based on an administrative database. Comorbidities and co-medication were coded at the time of the index event. There was no defined look-back period. However, the coding system (*ICD-10*) is maintained by physicians, and is precise and with high accuracy. We only assessed all-cause mortality and did not differentiate between different causes of death from different comorbidities. We documented aspirin–dipyrone and aspirin-alone but not dipyrone-alone medication. The rare but severe adverse drug reaction of agranulocytosis was not registered, even though an occurrence is unlikely in 5943 patients, because numbers range ≈1 case in 1 million patients.[57] Oral anticoagulation as co-medication was not assessed; however, atrial fibrillation as a disease with an indication for oral anticoagulation was analyzed (see section Results - Patients, and Table 2).

In observational pharmacoepidemiology, it is not possible to account completely for differences in patient disease severity, as perceived by the prescribing physician (indication bias); however, IPTW does remove a substantial portion of confounding of this type. Furthermore, it is a strength within pharmacoepidemiology that the comparison is of aspirin plus dipyrone to aspirin alone within a group of people for whom the initial diagnosis is relatively homogeneous.

Generally, patients' compliance could not be assured. Nevertheless, only patients with uninterrupted prescription of aspirin/dipyrone were included in this analysis. Because patients had to cover costs of drugs partially, high compliance seems likely. Finally, medication before the index event was not known. Therefore, the cohort consisted of prevalent users and new users for both aspirin and dipyrone.

CONCLUSIONS

In this observational, nationwide analysis, aspirin–dipyrone co-medication is associated with excess mortality. Therefore, dipyrone should be used with caution in aspirin-treated patients for secondary prevention. Optimal pain management or alternative antithrombotic strategies in these patients are urgently needed.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology, Pulmonology, and Vascular Medicine, Cardiovascular Research Institute Düsseldorf (A.P., L.D., C.H., M.P., D.M., P.M., S.Z., K.T., C.J., T.Z., M.K.), Institute of Molecular Medicine III, University Hospital Dusseldorf (B.L.) and Institute for Pharmacology and Clinical Pharmacology (K.S., T.H.), Heinrich Heine University Medical Center Düsseldorf, Düsseldorf, Germany; Institute for Clinical Pharmacology, University Medical Center Göttingen, Georg-August University, Göttingen, Germany (C.D.); Department of Medicine and Health Services Research, BARMER Statutory Health Insurance Fund, Wuppertal, Germany (U.M., H.L., B.H.); and Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Ludwig-Maximilians-University Munich, Munich, Germany (T.P.).

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Disclosures

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