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Pain is prevalent among patients with diabetes and chronic kidney disease (CKD). The management of chronic pain in these patients is limited by nephrotoxicity of commonly used drugs including non-steroidal anti-inflammatory drugs (NSAIDs) and opioids. Since previous studies implicated endothelin-1 in pain nociception, our *post hoc* analysis of the SONAR trial assessed the association between the endothelin receptor antagonist atrasentan and pain and prescription of analgesics. SONAR was a randomized, double-blind, placebo-controlled clinical trial that recruited participants with type 2 diabetes and CKD (estimated glomerular filtration rate 25–75 ml/min/1.73 m^2; urinary albumin-to-creatinine ratio 300–5000 mg/g). Participants were randomized to receive atrasentan or placebo (1834 each arm). The main outcome was pain-related adverse events (AEs) reported by investigators. We applied Cox regression to assess the effect of atrasentan compared to placebo on the risk of the first reported pain-related AE and, secondly, first prescription of analgesics. We used the Anderson-Gill method to assess effects on all (first and subsequent) pain-related AEs. During 2.2-year median follow-up, 1183 pain-related AEs occurred. Rates for the first pain-related event were 138.2 and 170.2 per 1000 person-years in the atrasentan and placebo group respectively (hazard ratio 0.82 [95% confidence interval 0.72–0.93]). Atrasentan also reduced the rate of all (first and subsequent) pain-related AEs (rate ratio 0.80 [0.70-0.91]). These findings were similar after accounting for competing risk of death (sub-hazard ratio 0.81 [0.71–0.92]). Patients treated with atrasentan initiated fewer analgesics including NSAIDs and opioids compared to placebo during follow-up (hazard ratio = 0.72 [0.60–0.88]). Thus, atrasentan was associated with reduced pain-related events and pain-related use of analgesics in carefully selected patients with type 2 diabetes and CKD.

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KEYWORDS: analgesics; atrasentan; chronic kidney disease; diabetes; nonsteroidal anti-inflammatory drug; opioids; pain

Lay Summary

Pain is common in patients with type 2 diabetes and chronic kidney disease (CKD). Therapies to treat pain, such as non-steroidal anti-inflammatory drugs, are often not safe in patients with CKD. Previous studies have suggested that endothelin-1 is involved in pain signaling. In this study, we demonstrate that the inhibition of endothelin-1 with the endothelin receptor antagonist atrasentan reduced the incidence of pain-related adverse events in patients with type 2 diabetes and CKD. These results support the conduct of a dedicated prospective clinical trial to confirm the possible benefits of atrasentan treatment on pain management in individuals with CKD.

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Pain is a common debilitating condition that affects many patients with diabetes and chronic kidney disease (CKD). Previous studies reported that 48% to 63% of patients with type 2 diabetes have pain symptoms, including

burning, numbness, tingling, fatigue, cramping, and aching.[1–4] The pathophysiology of pain is multifactorial and can be generally classified into nociceptive, neuropathic, or of mixed etiology.[5,6] Non-neuropathic pain is most commonly reported in patients with diabetes, with an incidence twice as high as that of neuropathic pain.[3,7] In patients with CKD, ∼60% of patients experience pain, of which musculoskeletal pain is the most common.[8] Pain is associated with reduced quality of life, in particular depression, poor sleep, and anxiety in patients with diabetes and CKD.[2,4,9–11]

The most often used analgesics for pain in patients with CKD include paracetamol, nonsteroidal anti-inflammatory drugs (NSAIDs), and opioids.[5] The management of pain in patients with diabetes and CKD is complicated as commonly used agents, including NSAIDs and opioids, increase the risk of acute kidney injury, CKD progression, and mortality even when used for short periods of time.[12–15] Therefore, therapeutic options for effective pain management in patients with diabetes and CKD are limited.

Endothelin-1 (ET-1) is a potent endogenous pluripotent peptide produced in response to tissue injury, mechanical stress, hypoxia, and inflammation.[16–18] Both ET-1 and its receptors are widely expressed throughout the body, including nociceptors along the peripheral and central pain neuronal pathways.[17,19] Systemic ET-1 levels increase in pain-dominated conditions such as musculoskeletal pain and arthritis. ET-1 stimulates and sensitizes pain sensation via endothelin receptor A and B.[17,20,21]

ET-1 is also implicated in the progression of CKD. Various clinical trials demonstrated that endothelin receptor antagonists reduce albuminuria.[22–24] The Study Of diabetic Nephropathy with AtRasentan (SONAR) trial demonstrated that the endothelin receptor A antagonist atrasentan reduced the risk of major kidney outcomes in patients with type 2 diabetes and CKD.[25] In this *post hoc* analysis of the SONAR trial, we assessed the association between atrasentan and pain-related adverse events (AEs) and the initiation of systemic analgesics.

METHODS

Design and participants

The SONAR trial was a randomized, double-blind, placebo-controlled clinical trial conducted at 689 clinical practice sites in 41 countries. The trial protocol, rationale of design, and primary results have been published.[25,26] Briefly, patients aged 18 to 85 years with type 2 diabetes, CKD (estimated glomerular filtration rate [eGFR] 25–75 ml/min per 1.73 m^2 and urine albumin-to-creatinine ratio [UACR] 300–5000 mg/g), and a brain natriuretic peptide concentration of ≤200 pg/ml were enrolled. eGFR was estimated by the CKD Epidemiology Collaboration (CKD-EPI) equation. Key exclusion criteria included history of hospitalized heart failure, severe peripheral or facial edema, type 1 diabetes, known nondiabetic kidney disease, pulmonary hypertension, pulmonary fibrosis, or any pulmonary diseases requiring oxygen therapy.

After screening and a run-in period to optimize background treatment with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, eligible patients received 0.75 mg of atrasentan once daily during the 6-week response enrichment period, aimed to select patients who were likely to respond to atrasentan, defined as an UACR reduction of ≥30%, and to exclude patients who were prone to atrasentan-induced fluid retention, defined as an increase of ≥3 kg in body weight or an increase in brain natriuretic peptide concentration to ≥300 pg/ml. All responder patients who tolerated atrasentan and a selection of nonresponder patients subsequently proceeded to the randomization visit and were assigned in a 1:1 ratio to either continue atrasentan 0.75 mg/d or to transition to placebo. The median total follow-up period was 2.2 years until the last trial visit (either in-clinic or telephone), which occurred by 29 March 2018.[25] The trial was approved by central or local ethics committees at all study sites before commencement of any study procedures and overseen by an independent data safety monitoring board.

Randomization

Randomization was performed centrally through an interactive voice response system on the basis of a computer-generated randomization schedule. A stratified randomization scheme was used to ensure balance in treatment allocation within geographic regions and baseline UACR levels (≤1000 or >1000 mg/g). Additionally, randomization was stratified by UACR change from baseline during the response enrichment period—≤−60%, >−60% to ≤−45%, >−45% to ≤−30% (classified as UACR responders) and >−30% to ≤−15%, >−15% to ≤0%, >0% (classified as UACR non-responders)—to assess whether the effect of atrasentan compared to placebo on the primary kidney outcome depended on the UACR change during response enrichment.

Outcome measures

The primary outcome of this *post hoc* analysis was pain-related AEs including serious AEs. All pain-related (serious) AEs, and the corresponding dates of onset, were reported by participating investigators. All AEs were assessed and categorized using the predefined standardized Medical Dictionary for Regulatory Activities queries. The severity of pain was determined by the site investigators who were blinded to randomized treatment allocation. Because the analyses focused on the incidence of chronic pain, we excluded surgical, injury, and infection pain-related AEs (e.g., fracture) from the primary analysis owing to their distinct and acute etiologies. A sensitivity analysis including all pain-related AEs irrespective of etiology was performed. Pain-related AEs as reported by investigators and categorized according to the Medical Dictionary for Regulatory Activities are provided in Supplementary Table S1.

The secondary outcome was the initiation of concomitant medications used to treat pain symptoms. Concomitant medications at baseline and during follow-up were also reported by site investigators. Records of analgesics including NSAIDs and opioids were identified using the anatomical therapeutic chemical classification. Pain-related prescriptions of analgesics were identified by the indication of each prescription. Systemic prescriptions of analgesics via oral, s.c., i.v., i.m., and rectal route (including buccal, sublingual, and transdermal) were included. Topical use was excluded in the main analysis as systemic absorption is low but included in a sensitivity analysis.[27] Surgery-, injury-, and infection-related prescriptions of analgesics were excluded in the main analysis but included in a sensitivity analysis.

Statistical analysis

We performed all statistical analyses in the intention-to-treat principle. We compared baseline characteristics using the unpaired *t* test,

Mann-Whitney test, or chi-square test, where appropriate. We plotted survival curves using Kaplan-Meier estimators and applied proportional hazards (Cox) regression models to assess the effect of atrasentan compared to placebo on the risk of the first reported pain-related AE. A competing risk analysis was also performed against mortality. We used the same model to assess the effect of atrasentan compared to placebo on the likelihood for the first prescription of analgesics. Participants who were using these medications at baseline were excluded from the analysis ($n = 717$). We also assessed the initiation of NSAIDs or opioids during follow-up in those not using each of these agents at baseline. For patients who had multiple events during follow-up, time to the first respective end point was used in each analysis. Patients with pain before randomization were not excluded, as there was no systematic assessment for pain for all patients at baseline. We performed analysis in the entire trial population and in baseline prespecified derived subgroups: age (<65 or ≥65 years), gender, race (Asian, Black, White, and other), UACR (<1000 or ≥1000 mg/g), eGFR (<45 or ≥45 ml/min per 1.73 m^2), as well as in *post hoc* derived subgroups: history of neuropathy or use of analgesics.

We compared the risks of all (first and subsequent) pain-related AEs between randomized groups in a time-to-event analysis by using the Anderson-Gill method.[28] In this analysis, we defined a recurrent pain–related AE when the occurrence was >90 days apart from the preceding event or a complaint of different nature. When no end date was reported, we imputed the date of the last observation. To account for the competing risk of death from any cause, we performed a companion analysis according to the method described by Fine and Gray.[29]

We performed sensitivity analyses to assess the robustness of the result. First, we included surgical, injury, and infection pain-related AEs in a sensitivity analysis. Second, we removed patients from the main analysis who were using analgesics at baseline. Third, in the recurrent pain analysis, we excluded patients without an event end date. Moreover, we removed the requirement of a 90-day interval between 2 subsequent pain-related AEs in the recurrent pain analysis. We also used Poisson regression to estimate the incidence rate ratio of pain-related AEs between treatment groups. For the initiation of analgesics, we excluded initiation of transdermal analgesics use. In the final sensitivity analysis on the initiation of NSAIDs or opioids, we not only excluded patients who were using NSAIDs or opioids at baseline but also excluded patients using any kind of analgesics.

A P value of < 0.05 was considered as statistically significant. R 4.2.0 (R Core Team) was used for all statistical analyses.

RESULTS

A total of 3668 patients were randomized to receive atrasentan ($n = 1834$) or placebo ($n = 1834$) in the double-blind phase and were included in the analysis. The baseline characteristics including known history of neuropathy and use of analgesics (including NSAIDs and opioids) were balanced between groups (Table 1). At baseline, 352 (19.2%) and 365 (19.9%) patients in the atrasentan and placebo groups were using analgesics.

During a median follow-up period of 2.2 years, a total of 1479 pain-related AEs unrelated to surgery, injury, or infection were reported, of which 103 were classified as serious AEs. Among these, 1183 pain-related AEs (atrasentan: 530; placebo: 653) were at least 90 days apart. Overall, 936 (25.5%) patients had at least 1 pain-related AE and 191 (5.2%) had ≥2 pain-related AEs.

Table 1 | Baseline characteristics

Characteristic	Atrasentan	Placebo
No. of patients	1834	1834
Age, yr	64.6 ± 8.8	64.4 ± 8.7
Gender: female	458 (25.0)	488 (26.6)
Race		
Asian	589 (32.1)	609 (33.2)
Black	109 (5.9)	115 (6.3)
Other	70 (3.8)	66 (3.6)
White	1066 (58.1)	1044 (56.9)
Body weight, kg	85.4 ± 20.0	85.1 ± 18.9
Body mass index, kg/m^2	30.4 ± 6.2	30.3 ± 6.4
History of diabetes, yr	16.5 ± 8.9	16.6 ± 9.0
Blood pressure, mm Hg		
Systolic	137.3 ± 14.9	137.0 ± 15.0
Diastolic	75.3 ± 9.8	75.2 ± 9.7
Glycated hemoglobin, %	7.6 ± 1.4	7.6 ± 1.5
eGFR, ml/min per 1.73 m^2	42.3 ± 12.9	41.9 ± 12.6
<45	1118 (61.0)	1149 (62.6)
≥45	716 (39.0)	685 (37.4)
UACR, mg/g	838.0 (473.2–1564.0)	826.0 (448.2–1553.0)
<1000	1062 (57.9)	1065 (58.1)
≥1000	772 (42.1)	768 (41.9)
Hemoglobin, g/l	129.9 (17.3)	128.6 (16.9)
Insulin use	1164 (63.5)	1151 (62.8)
Smoking history	302 (16.5)	270 (14.7)
CVD history	265 (14.4)	290 (15.8)
Known history of diabetic neuropathy[a]	5 (0.3)	6 (0.3)
Known history of neuropathy[a]	13 (0.7)	15 (0.8)
Analgesic use[b]	352 (19.2)	365 (19.9)
NSAIDs	63 (3.4)	70 (3.8)
Opioids	111 (6.1)	106 (5.8)

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; NSAID, nonsteroidal anti-inflammatory drug; UACR, urine albumin-to-creatinine ratio.
[a]History of neuropathy and diabetic neuropathy was assessed on the basis of adverse event complaints during the enrichment phase.
[b]All analgesics used for chronic pain management (excluding pain medication used for the treatment of other symptoms including surgery-related pain control, fracture, injury, and infection).
Data are expressed as mean ± SD or n (%). UACR is reported as median (25th–75th percentile).

In the atrasentan group, 429 (23.4%) patients had at least 1 pain-related AE, yielding an event rate of 138.2 events per 1000 person-years; the equivalent number in the placebo group was 507 (27.6%) patients, yielding an event rate of 170.2 events per 1000 person-years, resulting in a hazard ratio (HR) of 0.82 (95% confidence interval [CI] 0.72–0.93) for the first pain-related episode (Figure 1a). Compared with placebo, atrasentan also reduced the risk of all (first and subsequent) pain-related AEs (rate ratio [RR] 0.80; 95% CI 0.70–0.91; Figure 1b). These findings were also similar after accounting for the competing risk of death (sub-HR 0.81; 95% CI 0.71–0.92).

Considering the first pain-related AEs, atrasentan reduced the risk of incident musculoskeletal pain (HR 0.73; 95% CI 0.60–0.89), headache (HR 0.61; 95% CI 0.40–0.94), and spinal cord and nerve root disorder–related symptoms (HR 0.46; 95% CI 0.23–0.91; Figure 2). The HRs for pain with mild and moderate intensity were 0.82 (95% CI 0.71–0.96) and 0.90

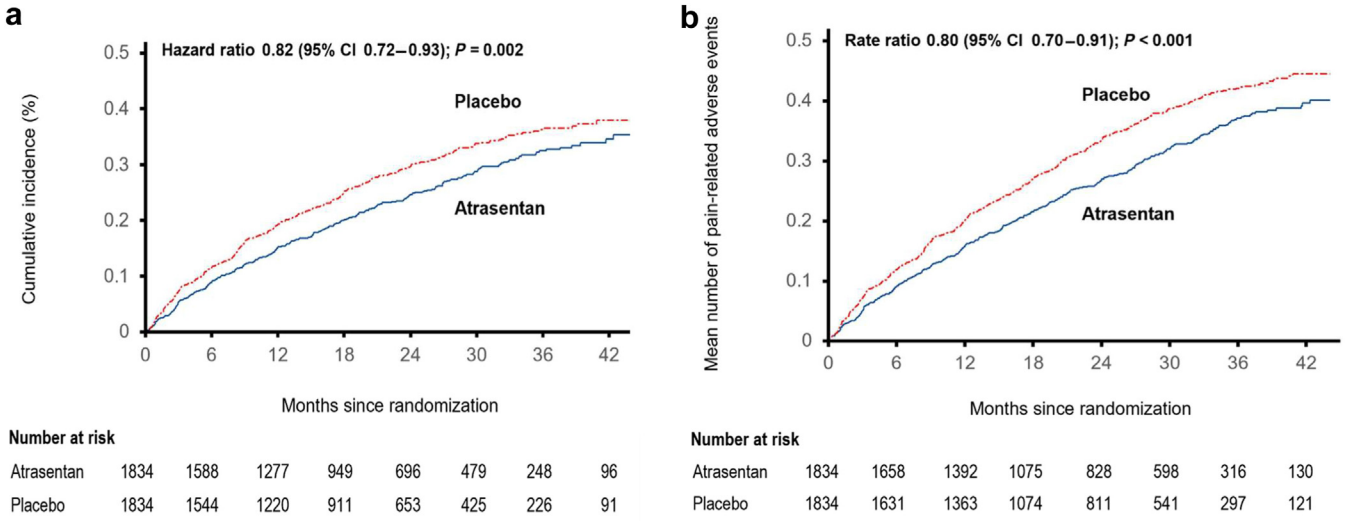

Figure 1 | Cumulative incidence of pain-related adverse events. (**a**) The first pain-related adverse events of all randomized patients are included. Surgery-, injury-, and infection-related pain events are excluded. (**b**) Cumulative incidence of recurrent pain–related adverse events. We defined a recurrent pain–related adverse event when the occurrence was >90 days apart from the preceding event or a complaint of different nature. CI, confidence interval.

(95% CI 0.73–1.11), respectively (Supplementary Figure S1). No statistically significant between-group differences were observed for other causes of pain-related AEs, including peripheral neuropathies (Figure 2). There was no evidence that the effects of atrasentan on first and all pain-related AEs varied by baseline eGFR (≥45 or <45 ml/min per 1.73 m^2), UACR (<1000 or ≥1000 mg/g), or other baseline characteristics (Figure 3).

Among participants not using analgesics at baseline, 177 (11.9%) in the atrasentan group and 235 (16.0%) in the placebo group initiated an analgesic during follow-up, resulting in an HR of 0.72 (95% CI 0.60–0.88; Figure 4). The effect of atrasentan compared to placebo was consistent for different analgesics with fewer NSAIDs (77 patients vs. 108 patients; HR 0.70; 95% CI 0.52–0.94) and opioids (89 patients vs. 107 patients; HR 0.83; 95% CI 0.62–1.10). The effect of atrasentan on the initiation of analgesics was comparable across subgroups (Supplementary Figure S2).

The results of the sensitivity analyses are reported in Supplementary Table S2 and Supplementary Figures S3 to S5. Results remained essentially similar for the pain analysis when surgery-, injury-, and infection-related events were included (Supplementary Figure S3) or when patients using analgesics at randomization were excluded. A further analysis with Poisson regression provided similar results (Supplementary Figure S4). Results also did not change for the medication analysis when

	Atrasentan		Placebo			
Category of pain	Incident pain	Percentage of patients	Incident pain	Percentage of patients	Hazard ratio (95% CI)	P
Musculoskeletal and connective tissue disorders	170	9.3%	228	12.4%	0.73 (0.60–0.89)	0.002
Joint disorders	139	7.6%	165	9.0%	0.83 (0.66–1.04)	0.105
Peripheral neuropathies	66	3.6%	55	3.0%	1.20 (0.84–1.72)	0.313
General system disorders	44	2.4%	46	2.5%	0.95 (0.63–1.43)	0.799
Headaches	34	1.9%	55	3.0%	0.61 (0.40–0.94)	0.024
Gastrointestinal signs and symptoms	39	2.1%	43	2.3%	0.90 (0.58–1.39)	0.632
Muscle disorders	15	0.8%	34	1.9%	0.43 (0.24–0.80)	0.007
Spinal cord and nerve root disorders	12	0.7%	26	1.4%	0.46 (0.23–0.91)	0.025

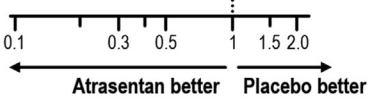

Figure 2 | Hazard ratio of different pain-related adverse event categories. The hazard ratio of incident pain–related adverse events by pain categories. Pain adverse events were categorized by higher level group term in blinded manner during the trial. Hazards of musculoskeletal and connective tissue disorders, headaches, muscle disorders, and spinal cord and nerve root disorders were reduced with atrasentan. Only pain events with incidence >1% are shown. CI, confidence interval.

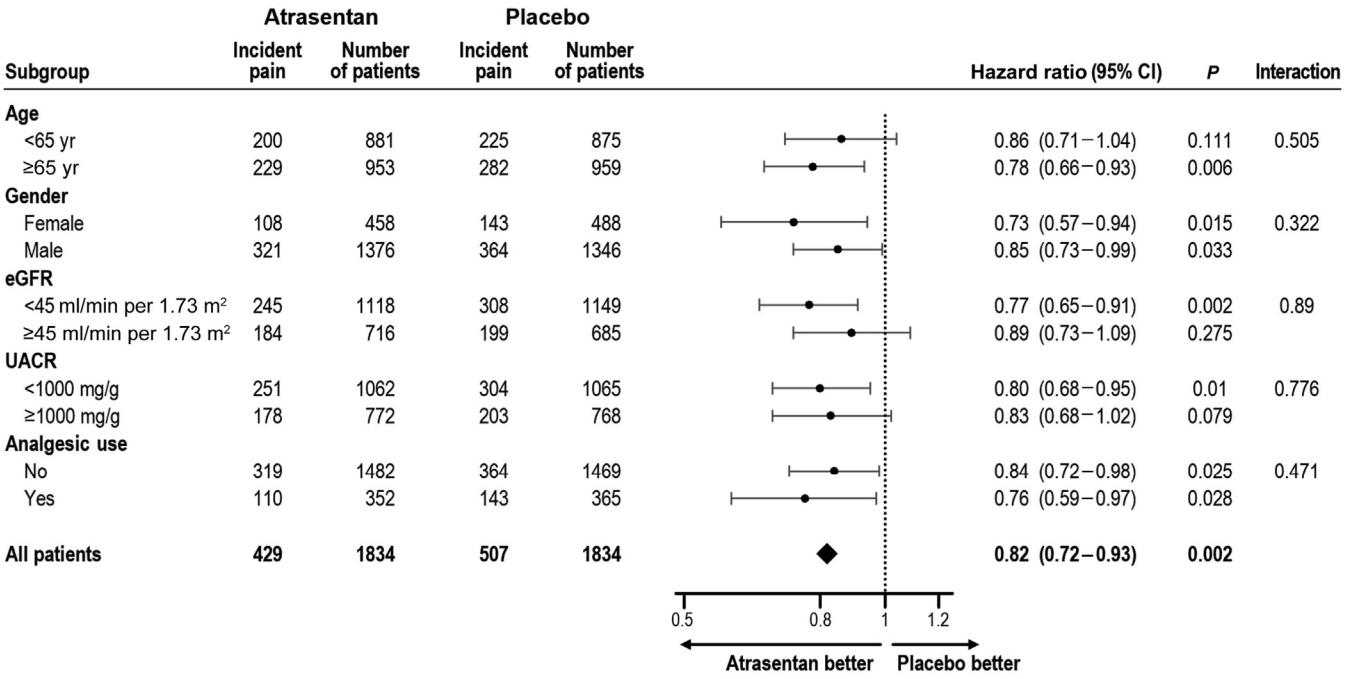

Figure 3 | Subgroup analysis of the hazard of incident pain. CI, confidence interval; eGFR, estimated glomerular filtration rate; UACR, urine albumin-to-creatinine ratio.

transdermal analgesics were excluded or when patients using any kind of analgesics were excluded for the analysis of the initiation of NSAIDs or opioids. (Supplementary Table S2 and Supplementary Figure S5).

DISCUSSION

Endothelin receptor antagonists have been shown to ameliorate pain-related symptoms in experimental and small clinical studies. In this *post hoc* analysis of the SONAR trial, we found that the endothelin receptor A antagonist atrasentan compared to placebo was associated with a significantly reduced number of pain episodes and initiation of common analgesics to relieve pain in patients with type 2 diabetes and CKD. These findings are clinically relevant as pain episodes are common in this population and reduce the quality of life. In addition, many of the commonly used analgesics for pain management are nephrotoxic and should be avoided, leaving this population with few effective therapies to manage pain.

Consistent with prior studies reporting a high prevalence and incidence of pain in patients with diabetes or CKD, in the SONAR trial, despite optimal guideline-recommended treatments, nearly 1 of 4 placebo-treated patients reported a pain-

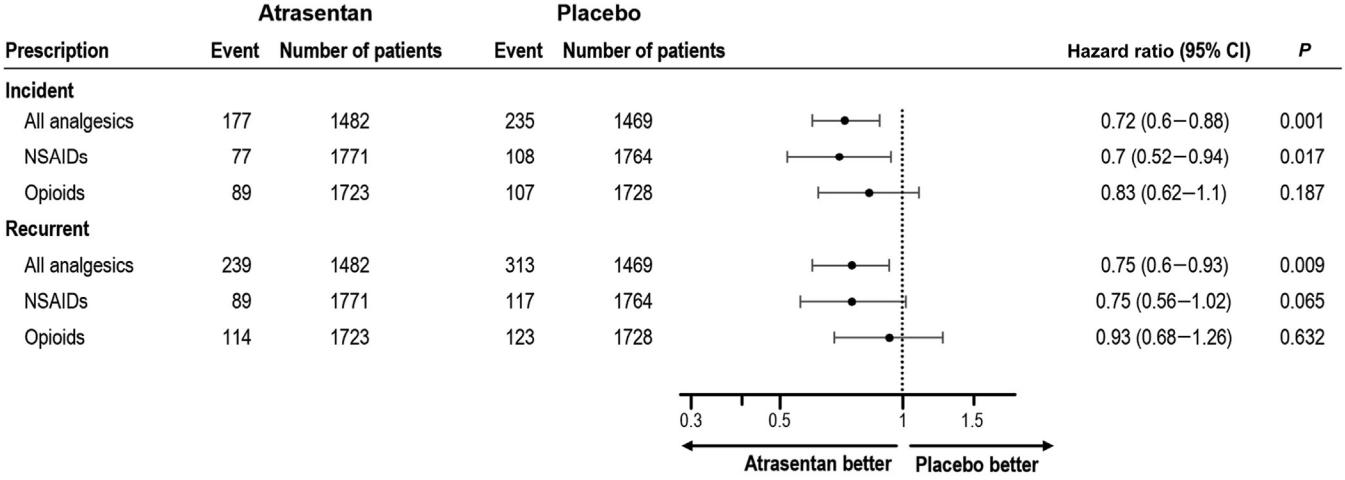

Figure 4 | Initiation of pain medications during follow-up. Initiation of analgesic medications in all randomized patients not using these medications at baseline. Analgesic prescriptions for surgery-, injury-, and infection-related analgesic prescriptions are excluded. Any pain medication that was different or 90 days apart from preceding prescription is regarded as a separate prescription. For recurrent event analysis, rate ratios are reported. NSAID, nonsteroidal anti-inflammatory drug.

related AE during a 2.2-year median double-blind treatment period. The high incidence of pain in these patients impairs life participation and control over health. A survey in 101 patients with CKD and 33 health care professionals reported that, although patients consistently ranked kidney function and mortality as the most important outcomes of kidney disease, patients also prioritized adverse outcomes that they cannot control such as joint and muscle pain.[30]

ET-1 has been implicated in the transmission of pain through activation of nociceptors and potentiation of other algogens such as capsaicin and arachidonic acid. In clinical studies, arterial administration of ET-1 caused muscular pain while dermal administration of ET-1 produced spontaneous pain and mechanical hyperalgesia.[31,32] ET-1 is also involved in inflammatory pain. ET-1 is released by various pro-inflammatory cells and causes nociception via different receptors, depending on the type of inflammation.[33,34] A common inflammatory pain condition is arthritis. A cross-sectional study reported higher ET-1 levels in patients with rheumatoid arthritis than in age- and gender-matched healthy controls. In animal models of arthritis-related pain, endothelin receptor antagonists alleviated pain induced by arthritis.[35,36] In the SONAR trial, atrasentan compared with placebo treatment reduced the incidence of pain related to joint and musculoskeletal disorders, supporting these prior experimental and clinical observations.

Neuropathy is a common complication of diabetes and can manifest as a painful syndrome. In a streptozotocin-induced diabetes animal model, acute and chronic administration of atrasentan reduced tactile allodynia, the perception of pain in response to normally nonpainful stimulation, a common complication of diabetic neuropathy.[37] Chronic administration of an endothelin receptor antagonist reduced tactile allodynia, suggesting a role for ET-1 in diabetic neuropathy–related pain. This notion is supported by an observational study in 2057 participants with type 2 diabetes, demonstrating that higher ET-1 levels were independently associated with a higher incidence of diabetic peripheral neuropathy.[38] In contrast to these studies, we did not observe a reduction in pain owing to peripheral neuropathies, including diabetic neuropathy in the SONAR trial. Whether the experimental models of diabetic neuropathy incorrectly reflect the human situation or whether the neutral results from our *post hoc* findings are inaccurate remains to be elucidated. It is also possible that diabetic neuropathy involves permanent nerve lesions and impaired signal transduction, a pathophysiological condition not targeted by the endothelin system.

The current pain therapies are often inadequate and contraindicated in patients with CKD because of side effects that cause kidney injury. Consistent with the incidence of pain episodes in our study, non-neuropathic pain is more common in patients with CKD, and these patients are more often prescribed analgesics compared with those having neuropathic pain.[7] A registry study in the United States previously reported that patients with CKD more frequently use nephrotoxins, including NSAIDs, than kidney protective drugs such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, highlighting the frequent use of these nephrotoxins and the dilemma clinicians face when managing these patients.[39] In our cohort, 19.5% of patients were using analgesics at entry into the trial supporting the previously observed frequent use of analgesics and the need for other effective medications to relieve pain. Importantly, the effect of atrasentan on pain-related AEs was not explained by the differential concomitant use of analgesics. In fact, the reduction in the risk of pain with atrasentan was observed despite more frequent initiation of pain medication over time in the placebo group, which would be expected to relieve pain and limit our ability to detect a beneficial effect of atrasentan.

This study should be interpreted in light of certain limitations. First, the result from this *post hoc* analysis should be interpreted as hypothesis-generating and is prone to chance findings. Second, although double-blinded pain-related AE and prescription data were available in the original data set, pain was not a predefined outcome of interest and there may be a reporting error as direct assessment of pain events using pain scales or questionnaires was not available. The baseline status of pain was not systematically assessed, and there may be a measurement error. However, it is likely that any potential measurement error is nonsystematic as the cohort was randomized and followed in a double-blind fashion. Third, we could not assess the use of over-the-counter acquired analgesics. In addition, the decision to initiate analgesics such as NSAIDs may be affected by the eGFR of the patient and not only by the onset and severity of chronic pain. Lastly, because the SONAR trial recruited carefully selected patients with type 2 diabetes and CKD, this limits the generalizability of our results to the general population with type 2 diabetes and CKD.

In conclusion, the endothelin receptor A antagonist atrasentan was associated with reduced pain-related events and pain-related use of analgesics in carefully selected patients with type 2 diabetes and CKD. Dedicated clinical trials are necessary to elucidate and confirm possible benefits of endothelin receptor antagonist treatment of pain management in individuals with CKD.

DISCLOSURE

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Pharmaceuticals, ProKidney, Otsuka Pharmaceuticals, Visterra, and Zai Lab; has received speaker honoraria from AstraZeneca, Baxter Healthcare, Boehringer Ingelheim, Chinook Therapeutics, and Otsuka Pharmaceuticals and has served as a member of data safety and monitoring committees for Dimerix and Zai Lab. SCWT has served as a consultant and advisory board member for Eledon Pharmaceuticals and has received speaker honoraria from AstraZeneca, Baxter Healthcare, Boehringer Ingelheim, and Novartis. DdZ has served as a member of advisory boards and/or speaker for Bayer, Boehringer Ingelheim, Fresenius, and Travere Pharmaceuticals; as a member of steering committees and/or speaker for AbbVie and Janssen; and as a member of Data Safety and Monitoring Committee for Bayer. All the other authors declared no competing interests.

DATA STATEMENT

The original clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research and will be provided after review and approval of a research proposal and Statistical Analysis Plan and execution of a Data Sharing Agreement by AbbVie and the corresponding author. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered.

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ROLE OF THE FUNDER

The funder (AbbVie) participated in the study design and data collection of the SONAR trial, but was not involved in the design, analysis, interpretation, and writing of the current *post hoc* analysis. The decision to submit the manuscript for publication was made jointly by all authors.

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AUTHOR CONTRIBUTIONS

HJLH, DEK, and DdZ were involved in the design of the study. HJLH, DEK, DdZ, AL, SCWT, RTG, and CW were involved in the collection of data. KWC, JDS, and MS analyzed the data. KWC, JDS, and HJLH wrote the first draft of the article. All authors were involved in data interpretation and in drafting and critically revising the article. The lead and corresponding author had access to study results, and the lead author takes responsibility for the integrity of the data and accuracy of the data reported. All authors reviewed and approved the final version of the article for submission.

SUPPLEMENTARY MATERIAL

Supplementary File (Word)

Supplementary Table S1. List of included pain-related events by category.

Supplementary Table S2. Sensitivity analyses.

Supplementary Figure S1. Incidence of pain by severity.

Supplementary Figure S2. Subgroup analysis of the effect of atrasentan compared to placebo on the initiation of analgesics.

Supplementary Figure S3. Cumulative incidence of all-cause pain-related adverse events.

Supplementary Figure S4. Count of patients and pain-related events.

Supplementary Figure S5. Sensitivity analysis of the initiation of pain medications during follow-up.

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