Bisphosphonates and Glucose Homeostasis: A Population-Based, Retrospective Cohort Study

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Context: Evidence suggests that the human skeleton might be involved in the regulation of glucose homeostasis.

Objective: The objective of the study was to investigate the effect of exposure to bisphosphonates on the risk of incident type 2 diabetes mellitus (T2DM).

Design: This was a population-based, retrospective, open cohort study over the period 1995–2010.

Setting: The study was conducted from The Health Improvement Network database from the United Kingdom in a primary care setting.

Patients: A total of 35 998 individuals aged older than 60 years, without diabetes at baseline and with more than 1 year's exposure to bisphosphonates, and 126 459 age-, gender-, body mass index- and general practice-matched unexposed individuals participated in the study.

Interventions: There were no interventions.

Main Outcome Measure: A new diagnosis of T2DM during the 16-year-long observation period, determined by Read codes and adjusted incidence rate ratio in bisphosphonate-exposed compared with unexposed groups, was the main outcome measure.

Results: The risk of incident T2DM was significantly lower in patients exposed to bisphosphonates compared with matched controls [adjusted incidence rate ratio 0.52, 95% confidence interval (CI) 0.48–0.56, $P < .0001$]. In subgroup analyses, the findings remained consistent in males [0.77 (95% CI 0.66–0.89)], females [0.49 (95% CI 0.45–0.53)], obese [0.54 (95% CI 0.50–0.59)], individuals exposed to steroid treatment [0.47 (95% CI 0.34–0.64)], and over different types of bisphosphonate medication. Analysis of duration of treatment suggested a brief increase in the risk of T2DM (1 to 2.5 y of exposure), followed by a progressive, sustained decrease as the years of exposure accumulated.

Conclusions: This observational evidence suggests exposure to bisphosphonates was associated with a significant 50% reduction in the risk of incident T2DM. **(*J Clin Endocrinol Metab* 100: 1933–1940, 2015)**

Osteocalcin is an osteoblast lineage-derived secreted protein, forming the 1%–2% of the bone matrix. Its macromolecule is characterized by the presence of three calcium-binding carboxyglutamic residues. The degree of their carboxylation, ranging from fully carboxylated to the un(der)carboxylated form (uOC), determines the af-

ISSN Print 0021-972X ISSN Online 1945-7197
Printed in U.S.A.

Received September 11, 2014. Accepted February 9, 2015.
First Published Online February 19, 2015

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Abbreviations: aIRR, adjusted incidence rate ratio; BMI, body mass index; CI, confidence interval; GP, general practice; T2DM, type 2 diabetes mellitus; TOC, total osteocalcin; uOC, un(der)carboxylated form.

finity to the skeleton (1). In clinical practice, osteocalcin is an established biochemical marker of osteoblast activity (bone formation), and its measurement may be useful for monitoring the response to osteoporosis treatment (2).

On the basis of experimental evidence (3, 4), osteocalcin is believed to play a central role in regulating the cross talk between murine fuel and bone metabolism (5). In brief, skeleton-derived total osteocalcin (TOC) and particularly uOC have been shown to promote both insulin production and sensitivity (6), through concerted actions on the pancreatic β- and fat cells, respectively. The latter are thought to be mediated by adiponectin (7), potentially implying a differential effect on the basis of gender. Recent advances suggest that a forkhead family transcription factor (8–10) and the nuclear factor-κB signaling (11) are key players in the regulation and mediation of these effects, respectively, at the molecular level. Remarkably, osteocalcin has also been shown to promote pancreatic β-cell mass accrual (12).

The relevance of this novel skeleton/adipoinsular axis in humans is under active investigation. Both TOC and uOC were reported to be lower in patients with diabetes and inversely associated with a range of insulin resistance indices (1, 13, 14) as well as markers of dysmetabolic phenotype and adiposity (15–17). Lower TOC and/or uOC levels were associated with the incident risk of type 2 diabetes mellitus (T2DM) (18, 19) or changes in insulin sensitivity (20). On the other hand, these findings were not universally confirmed (21, 22).

Osteoclast-mediated bone resorption is thought to be required to decarboxylate TOC and release the metabolically active uOC into the systemic circulation. Bisphosphonates, potent inhibitors of osteoclastic activity, do suppress bone turnover and decrease systemic uOC levels (23, 24). Therefore, it would be plausible to assume that this decrease might have deleterious effects on energy metabolism (25, 26). In fact, the change in uOC was inversely associated with changes in fat parameters and positively associated with a change in adiponectin in postmenopausal women treated with alendronate (27). On the contrary, incident T2DM was found to be modestly lower in individuals treated with alendronate in a retrospective cohort study (28), and no significant change in glucose homeostasis was documented in a post hoc analysis of three major randomized trials of antiresorptive agents (29).

Although these findings collectively question the relevance of osteocalcin manipulation in the context of human glucose homeostasis, the clarification of its role is arguably further perplexed by study limitations, notably the confounding effect of obesity and the diagnosis/definition of T2DM, respectively. Moreover, the exploration of potential gender-specific effects (30) would further advance our understanding of the endocrine skeleton.

The prevalence of osteoporosis in England and Wales is significant (31), and more than a million patients were prescribed a bisphosphonate in the United Kingdom during 2009–2010 (32). Considering the widespread use of bisphosphonates in the treatment of osteoporosis, the potential ramifications of any effect (beneficial or detrimental) on the incidence of diabetes mellitus would be important from the public health perspective as well.

To address these considerations, we performed a retrospective open cohort study to determine the risk of developing T2DM in patients prescribed bisphosphonates compared with appropriately matched controls.

Materials and Methods

Study design

This was a population-based, retrospective, open cohort study in which patients exposed to bisphosphonates were compared with age-, gender-, body mass index (BMI)-, and general practice (primary care setting)-matched controls unexposed to bisphosphonates.

Source of data

Data were derived from The Health Improvement Network database. This is a database of anonymized electronic patient records contributed by general practices (GPs) using the Vision computer system. It includes records from more than 500 UK GPs (~11 million patients, of which 3 million are actively registered with their practices; http://csdmruk.cegedim.com/our-data/our-data.shtml).

Study cohort

The study period was set from first January 1995 (study start) to December 31, 2010 (study end). The study was an open cohort, and the date at which each individual joined the cohort is called their index date. All individuals in the study cohort were required to be registered at their practice at least 1 year before entry into the study to ensure that they were not previously exposed to bisphosphonates and did not have the outcome of interest prior to entry. Their practice was also required to have been using their computer system (Vision) for at least 1 year prior to their index date and have an Acceptable Mortality Rate (AMR) date (an indicator of practice data quality) prior to their index date in order to ensure that the practice was making full use of their system and not under-recording important outcomes (33).

Exposure

Individuals were included in the exposed cohort if they met the following criteria: 1) were aged 60+ years at the index date, 2) did not have a diagnosis of diabetes mellitus at the their index date, 3) had more than 1 year of treatment with a bisphosphonate (defined as one or more prescriptions for four consecutive quarters), and 4) remained at their practice at least 1 year after their index date.

The index date for each patient was the date at which the patient had at least 1 year's worth of bisphosphonate treatment. Duration of exposure was defined as the time period from the index date to the exit date or last prescription, whichever was the earliest.

Selection of controls

For each exposed patient, up to four unexposed controls were selected from patients registered in the same participating general practice. Controls were individually matched to cases on age at index date (to within 2 y) and gender; did not have a diagnosis of diabetes mellitus at their index date; were unexposed to bisphosphonates (fewer than one prescription in four successive quarters); and remained at their practice at least 1 year after their index date. Controls were also matched to BMI (to within 3 kg/m^2 if the BMI was recorded or matched to cases with missing BMI).

Follow-up

Exposed and unexposed patients were followed up (observation period) from the index date until the first of the following events (exit date): patient died; patient left practice; last data collection from practice; patient diagnosed with T2DM.

Outcome

The primary outcome was a new diagnosis of diabetes mellitus dated during the observation period. Secondary analyses were performed to detect age, gender, BMI, and medication-specific effects. Furthermore, the association between the duration of exposure to bisphoshonates and the incidence of T2DM was explored by stratifying the exposed cohort along with their respective matched controls into quartiles according to the duration of exposure. Diagnosis of diabetes mellitus were determined by Read codes (http://systems.hscic.gov.uk/data/uktc/readcodes) stemming from C10.

Covariates

Potential risk modifiers (confounders) were used as model covariates and were selected on the basis of biological plausibility and established epidemiological evidence relevant to the study population (34). These covariates were the presence of hypertension, cardiovascular disease (CVD), smoking status, deprivation quintile, and oral steroid treatment. The latter was defined as one or more prescriptions for four consecutive quarters during the year preceding the index date, whereas the recording at the index date was used for all other covariates.

Statistical analysis

The cohort's covariates and matching characteristics were summarized for those exposed and unexposed to bisphosphonates using appropriate descriptive statistics. Differences between exposed and unexposed groups were investigated using χ^2 tests (for categorical variables) and *t* tests or the Mann-Whitney *U* test for continuous variables.

We compared the incidence rate of T2DM between those exposed and unexposed. There is potential for immortal time bias (35) because exposed patients had to survive at least four quarters to be classified as exposed, whereas unexposed patients did not. To protect against immortal time bias, exposed patients were classified as exposed from the date of 1 year of usage and unexposed were matched on this date so start of follow-up is the same for both exposed and unexposed. To accommodate the clustered nature of the data, incident rate ratios were estimated using generalized linear mixed models (Poisson model with log link) with a random effect for GP practice and adjusting for patient level covariates (age, gender, BMI, presence of hypertension, smoking status, deprivation quintile, steroid treatment), offset by the person-years of exposure to determine whether the exposure to bisphosphonates was associated with development of T2DM after adjusting for other important prognostic factors. These analyses were repeated in a number of subgroups (males and females; BMI $\geq$ 25 kg/m^2 and BMI < 25 kg/m^2; steroid user and nonsteroid user). We also undertook an analysis to study the impact of the duration of treatment and the compound-specific effect on the incidence of T2DM.

To investigate whether undetected biases might have distorted the results, the procedure was repeated, following the same steps but using chronic obstructive pulmonary disease instead of T2DM as the main outcome and controlling for age, gender, smoking, and deprivation quintile.

All model assumptions were checked and statistical significance level was set at $P = .05$. Missing data were minimal and therefore were treated as missing categories [for BMI and deprivation index (Townsend Index)] in our analysis rather than data being excluded. All analyses were implemented in Stata 13.0.

Results

Cohort characteristics

Over the 16-year-long observation period, 162 447 individuals who met the selection criteria were identified. Of these, 35 998 subjects (22.2%) were exposed to bisphosphonates, whereas 126 459 subjects were unexposed and served as age-, gender-, BMI-, and GP-matched controls. The median follow-up period was approximately 42 months for the exposed group, which included more steroid users (16%) compared with controls (<1%). No difference was observed between groups in terms of prevalence of hypertension. Descriptive characteristics by exposure group are detailed in Table 1. In total, 6802 cases with newly diagnosed diabetes mellitus (956 from the exposed and 5846 from the matched control group) were recorded.

Risk of incident diabetes mellitus

The crude event rates were 6.55 and 12.16 per 1000 person-years for exposed patients and controls, respectively. After covariate adjustment, the risk of incident diabetes mellitus was significantly lower in patients exposed to bisphosphonates compared with matched controls [adjusted incidence rate ratio (aIRR) 0.52, 95% confidence interval (CI) 0.48–0.56, $P < .0001$, Table 2]. Our validation method using chronic obstructive pulmonary disease as an outcome did not show a significant association (aIRR 0.99; 95% CI 0.93–1.06).

Table 1. Baseline Characteristics of Cohort by Exposure Status to Bisphosphonates

	Unexposed (n = 126 459)	Exposed (n = 35 988)	P Value
Follow-up period years, median [IQR]	3.34 [1.99, 5.16]	3.59 [2.13, 5.59]	<.001
Age, y, mean (SD)	74.1 (8.5)	74.9 (8.5)	<.001
Male	21 908 (17.3%)	5767 (16.0%)	<.001
BMI, kg/m^2, mean (SD)	25.7 (4.4)	25.2 (4.9)	<.001
(missing)	3188	9546	
CVD[a]	22 893 (18.1%)	7262 (20.2%)	<.001
Hypertensive[a]	49 436 (39.1%)	14 043 (39.0%)	.807
Smoker[a]	15 880 (12.6%)	4132 (11.5%)	<.001
Steroid	980 (0.77%)	5736 (15.9%)	<.001
Townsend index (quintiles)[b]			
1	31 014 (24.5%)	8764 (24.4%)	.005
2	28 143 (22.3%)	8049 (22.4%)	
3	24 288 (19.2%)	6708 (18.6%)	
4	20 536 (16.2%)	5847 (16.3%)	
5	13 261 (10.5%)	3992 (11.1%)	
Not available	9217 (7.3%)	2628 (7.3%)	
Country			
England	103 496 (81.8%)	29 293 (81.4%)	.101
Northern Ireland	5052 (4.0%)	1517 (4.2%)	
Scotland	8979 (7.1%)	2640 (7.3%)	
Wales	8932 (7.1%)	2538 (7.1%)	

Abbreviations: CVD, cardiovascular disease; IQR, interquartile range. Values are numbers (percentages) unless otherwise specified. *P* values are from a χ^2 test for proportions or *t* test (for age and BMI) and Mann-Whitney *U* test for follow-up.

[a] For CVD, hypertensive- and smoker-positive documentation was considered as presence of the risk factor, and absence of any documentation was considered as no existence of these risk factors.

[b] A high Townsend Index is indicative of high material deprivation. The index is assigned to each patient record based on their residential postal code.

Gender-specific effects

Female patients exposed to bisphosphonates were found to be 50% less likely to develop diabetes mellitus compared with female controls (aIRR 0.49, 95% CI 0.45–0.53, $P < .0001$, Table 2). Similarly, the difference in the risk of incident diabetes mellitus between male patients exposed and unexposed to bisphosphonates was significant, but the effect size was lower (aIRR 0.71, 95% CI 0. 0.59–0.85, $P < .0001$, Table 2).

Subgroup analyses

In overweight and obese subjects, the risk of incident T2DM was lower in those exposed to bisphosphonates compared with controls (aIRR 0.54, 95% CI 0.50–0.59, $P < .0001$, Table 2). An effect of similar magnitude and direction was also noted in lean subjects (aIRR 0.44, 95% CI 0.38–0.52, $P < .0001$, Table 2). The effect of bisphosphonates on the risk of incident T2DM was also similar in those exposed and unexposed to glucocorticoid treatment (aIRR 0.47, 95% CI 0.34–0.64, $P = .001$, and aIRR 0.52, 95% CI 0.48–0.56, $P < .0001$, respectively, Table 2).

Compound-specific vs class effect

The risk of incident T2DM was significantly lower in those exposed to bisphosphonates compared with controls, independent of the specific agent used [alendronate, risedronate, etidronate, and other categories (zoledronate, ibandronate)]. The compound-specific outcomes, suggestive of a class effect, are summarized in Table 3.

Duration of exposure

The results of investigating the association between the duration of exposure (in quartiles) and the risk of incident diabetes mellitus are summarized in Table 4. In general, a consistent decrease in the risk of incident T2DM is noted as the years of exposure accumulate. In other words, the greater the duration of exposure, the lower the chance of developing diabetes mellitus. Interestingly, the risk of incident T2DM in the first quartile (1–2.52 y) was significantly higher in those exposed to bisphosphonates compared with the controls. In contrast, this risk was significantly lower in the exposed cohort in the subsequent quartiles.

Discussion

On the basis of the above epidemiological evidence from a large-scale, population-based study with an adequate follow-up period, careful matching, and covariate adjustment, we observed that patients exposed to bisphosphonates showed a significant 50% lower risk of developing

Table 2. Estimated Incidence Rate Ratio of Diabetes Mellitus by Exposure Status to Bisphosphonates

	Unexposed	Exposed	IRR (95% CI) and *P* Values	aIRR (95% CI) and *P* Values[a]
All cases				
	n = 126 459	n = 35 988		
DM cases	5846	956		
Person years	480 667.7	145 895.2	0.54 (0.50, 0.58) $P < .001$	0.52 (0.48, 0.56) $P < .001$
Subgroup analyses				
Males	n = 21 908	n = 5767		
DM cases	1060	208		
Person-years	81 206.05	20 823.6	0.77 (0.66,0.89) $P < .001$	0.71 (0.59, 0.85) $P < .001$
Females	n = 104 551	n = 30 221		
DM cases	4786	748		
Person years	399 461.7	125 071.6	0.50 (0.46,0.54) $P < .001$	0.49 (0.45, 0.53) $P < .001$
BMI ≥ 25 kg/m^2[b]	n = 81 425	n = 22 273		
DM cases	4639	779		
Person-years	310 726.1	91 291.9	0.57 (0.53, 0.62) $P < .001$	0.54 (0.50, 0.59) $P < .001$
BMI < 25 kg/m^2[b]	n = 45 034	n = 13 715		
DM cases	1207	177		
Person-years	169 941.6	54 603.2	0.46 (0.39, 0.53) $P < .001$	0.44 (0.38, 0.52) $P < .001$
Systemic steroid use	n = 980	n = 5736		
DM cases	52	227		
Person-years	3064.1	22 804.2	0.59 (0.43, 0.81) $P < .001$	0.47 (0.34, 0.64) $P < .001$
No use of systemic steroid	n = 125 479	n = 30 252		
DM cases	5794	729	0.49 (0.45, 0.53)	0.52 (0.48, 0.56)
Person-years	477 603.7	123 091.0	$P < .001$	$P < .001$

Abbreviations: DM, diabetes mellitus; IRR, incidence rate ratio.

[a] Adjusted for age, gender, BMI (treated as categories of < 20, 20–24.9, 25–29.9, 30–34.9, ≥ 35 kg/m^2, and missing group), cardiovascular disease, hypertension, smoking, steroid use, and deprivation quintiles.

[b] Analysis based on data that were available.

diabetes mellitus compared with matched controls. Moreover, this effect was shown to be independent of gender, BMI, glucocorticoid use, and specific compound, yet it might be related to the duration of exposure.

Other studies have investigated this relationship (28, 29). The first study to report the risk of incident T2DM in patients under osteoporosis medications suggested that alendronate, etidronate, and raloxifene use were associated with a lower risk of T2DM (28). However, these results were limited by being based solely on hospital discharge records and by the analysis, which was not controlled for obesity, and other potential important confounders. A post hoc analysis using data from three randomized controlled trials with antiresorptives (alendronate, denosumab, zoledronic acid) neither confirm the above risk reduction nor revealed an excess risk of incident diabetes (29). However, this study was again limited by the method used for outcome (T2DM) ascertainment (adverse event reports).

The magnitude of this effect (50% lower risk), the validation procedure, and the data source mean that these findings are unlikely to be due to confounding or other study biases. However, study limitations and other plausible explanations should be considered. In specific, the theoretical possibility of differentially increased weight gain in cohort groups or that of misclassifying patients with type 1 diabetes mellitus as T2DM and the potential effects of concomitant medications (such as β-blockers, statins, vitamin D supplementation, hormone replacement therapy) should be noted. More importantly, the suboptimal persistence with osteoporosis medications (36) and the intensity of exposure (dose related effects) were not captured in the present study design, and thus, relevant secondary analyses were not performed. We also were not able to include all important confounders such as family history of diabetes due to suboptimal documentation in the medical records.

Taking the above into consideration, it might be intriguing to suggest alternative hypotheses regarding the effect of bisphosphonates on the risk of incident T2DM. This effect may be explained by a favorable change in the uOC to TOC ratio, induced by long-term exposure to

Table 3. Estimated Incidence Based on the Specific Medication

	Unexposed	Exposed	IRR (95% CI) and *P* Values	Adjusted IRR (95% CI) and *P* Values[a]
Alendronate	n = 69 847	n = 19 916		
DM cases	2917	521		
Person-years	244 998.2	73 137.28	0.60 (0.54, 0.66) $P < .001$	0.58 (0.52, 0.64) $P < .001$
Risedronate	n = 16 829	n = 4863		
DM cases	696	105		
Person-years	60 854.28	17 408.59	0.53 (0.43, 0.65) $P < .001$	0.50 (0.40, 0.63) $P < .001$
Etidronate	n = 7282	n = 1995		
DM cases	502	79		
Person-years	38 908.8	11 147.6	0.55 (0.43, 0.69) $P < .001$	0.49 (0.38, 0.64) $P < .001$
Exposed to any other medication	n = 5148	n = 1466		
DM cases	173	26		
Person-years	14 788.1	3923.5	0.56 (0.37, 0.86) $P = .002$	0.56 (0.37–0.87) $P < .001$
Exposed to more than one medication	n = 27 353	n = 7748		
DM cases	1558	225		
Person-years	121 118.4	40 278.3	0.43 (0.38, 0.50) $P < .001$	0.43 (0.37–0.50) $P < .001$

Abbreviations: DM, diabetes mellitus; IRR, incidence rate ratio.

[a] Adjusted for age, gender, BMI (treated as categories of < 20, 20–24.9, 25–29.9, 30–34.9, ≥ 35 kg/m^2, and missing group), cardiovascular disease, hypertension, smoking, steroid use and deprivation quintiles.

bisphosphonates, and promoting insulin sensitivity. This assumption was investigated in a subset of postmenopausal osteoporotic women under treatment with alendronate for 3 months (27). This study showed that both uOC and TOC were decreased after the 3-month alendronate treatment and that the uOC to TOC ratio remained stable. However, the study sample size was small and the duration of treatment was short. Thus, we could speculate that bisphosphonates induce a short-term decrease in insulin sensitivity, followed by a compensatory increase, possibly mediated by corresponding changes in uOC to TOC ratio. Ultimately, a relatively higher decrease in TOC (compared with uOC), which would favor insulin sensitivity, might occur after a longer exposure to alendronate treatment. This would explain the brief increase in the risk of incident T2DM (1–2.5 y), followed by a sus-

Table 4. Risk of Incident Diabetes Mellitus in Subjects Under Bisphosphonate Treatment and Matched Controls on the Basis of Duration Of Exposure.

Duration of Treatment in Quartiles, y	Unexposed	Exposed	IRR (95% CI) and *P* Values	Adjusted IRR (95% CI) and *P* Values[a]
1–2.52	n = 31 206	n = 9005		
DM cases	977	406		
Person-years	86 637.86	20 552.15	1.75 (1.56–1.97) $P < .001$	1.67 (1.47, 1.90) $P < .001$
2.53–3.82	n = 31 315	n = 8986		
DM cases	1051	234		
Person-years	96 279.33	24 515.64	0.87 (0.76–1.01) $P = .063$	0.81 (0.69, 0.94) $P = .007$
3.83–5.77	n = 31 619	n = 8993		
DM cases	1379	207		
Person-years	125 559.6	37 776.5	0.50 (0.43, 0.58) $P < 0.001$	0.49 (0.42, 0.57) $P < 0.001$
Greater than 5.77	n = 32 319	n = 9004		
DM cases	2439	109		
Person-years	172 190.9	63 050.92	0.12 (0.10, 0.15) $P < 0.001$	0.13 (0.11, 0.16) $P < 0.001$

Abbreviations: DM, diabetes mellitus; IRR, incidence rate ratio.

[a] Adjusted for age, gender, BMI (treated as categories of < 20, 20–24.9, 25–29.9, 30–34.9, ≥ 35 kg/m^2, and missing group), cardiovascular disease, hypertension, smoking, steroid use, and deprivation quintiles.

tained decrease as the years of exposure accumulate. On the other hand, it should be noted that the observed increase in the risk of T2DM at the initial stage (1–2.5 y) might be the result of the increased number of contacts with the primary care setting (the chance of getting a health check including an assessment and testing for diabetes) for those diagnosed with osteoporosis and prescribed the medication as compared with the controls.

Alternative speculations regarding the effect of bisphosphonates on the risk of T2DM might also include the bisphosphonate-induced disruption of prenylation of small-molecular-mass G proteins (37), the reduction of the proinflammatory cytokines (IL-1 and IL-6) (38) or the presence of functional mutations in the receptor of gastric inhibitory polypeptide (39).

In summary, exposure to bisphosphonates may be associated with a significant reduction in the risk of incident T2DM and this class effect seems to be more pronounced in women. Considering the significant prevalence of osteoporosis and the widespread bisphosphonate use, the effect bisphosphonates might have on the risk of incident T2DM could be important at the population level and might constitute a major pharmacovigilance issue. Thus, this finding should be further investigated using both clinical and preclinical study designs. Although potential biases and other explanations for these findings must be investigated, evidence of a potential association between bisphosphonates and risk of diabetes mellitus would also provide an indirect confirmation of bone-energy axis in humans.

Acknowledgments

The views expressed in this publication are not necessarily those of the National Institute of Health Research, the Department of Health, National Health Service Partner Trusts, or the University of Birmingham.

Analysis of routine data for this study was approved by the Scientific Review Committee of the Cegedim Strategic Data Medical Research United Kingdom (The Health Improvement Network database data set provider).

The data are from The Health Improvement Network database. We are happy to share the extracted data on obtaining necessary approvals.

Contributions of the authors include the following: K.A.T. had the original research idea, which was further refined with K.N.. K.A.T. and K.N. are guarantors. K.N. developed the study design with contributions from K.H., R.R., T.M., and K.A.T. R.R. carried out the data extraction, and K.H. and K.N. analyzed the data. K.A.T. led the writing of the paper with contributions from K.N., K.H., T.M., and R.R. All authors contributed to the interpretation of the data and revision of the manuscript.

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This work was supported by the National Institute of Health Research School for Primary Care Research. T.M. is partially funded by the National Institute for Health Research (NIHR) Collaborations for Leadership in Applied Health Research and Care West Midlands. This paper presents independent research and the views expressed are those of the author(s) and not necessarily those of the National Health Service (NHS), the NIHR, or the Department of Health. K.H. had financial support from the Medical Research Council (MRC) Midland Hub for Trials Methodology Research (grant no. G0800808). R.R. and T.M. are also funded by the Heart of England NHS Foundation Trust.

Disclosure Summary: The authors have nothing to disclose.

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