Propranolol Reduces Risk of Knee or Hip Replacement Due to Osteoarthritis: a Propensity Score Matched Cohort Study-using Data From the Clinical Practice Research Datalink.

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Abstract

Objectives To examine the association between *β*-blocker prescription and knee or hip total joint replacement (TJR) in a UK primary-care population with incident knee or hip osteoarthritis (OA).

Methods Cohort study using data from the Clinical Practice Research Datalink. Participants aged ≥40 years with incident knee or hip OA, exposed to *β*-blockers after OA diagnosis (new-user design), were matched to one control for age, sex, OA location and propensity score (PS) for *β*-blocker prescription. Cox-proportional hazard ratios (HRs) and 95% confidence intervals (CI) were calculated. The analyses were adjusted for factors that influence health-seeking behaviour, progression of OA, and stratified according to *β*-blocker classification. Data analysis was conducted using Stata.

Results Data for 6,970 PS-matched *β*-blocker exposed and unexposed participants were included. Any *β*-blocker prescription was not associated with knee or hip TJR (aHR 1.11; 95% CI 0.98 – 1.25). However, prescription of lipophilic non-selective β-blockers having membrane stabilising effects associated with reduced risk of knee or hip TJR (aHR 0.69; 95% CI 0.52 – 0.93). Of these, there was a protective effect for propranolol (aHR 0.71; 95% CI 0.53 – 0.95), the commonest prescribed drug in this class. The number needed to treat (95% CI) with propranolol for two years in order to prevent one TJR was 32 (23-52).

Conclusion Propranolol, a non-selective β-blocker, reduces the risk of knee and hip TJR. This is consistent with its analgesic effects in other conditions and a randomised controlled trial is required to further evaluate its analgesic potential and safety in OA.

Key Message

What is already known about this subject?

- There is paucity of safe and effective analgesic drugs for OA.
- β-adrenoreceptor blockers have demonstrated anti-nociceptive effects in several painful conditions.

What does this study add?

- Propranolol, a non-selective β-blocker, reduces the risk of knee and hip TJR in people with OA.

How might this impact on clinical practice or future developments?

- Propranolol may be used as an analgesic for OA-pain if these findings are confirmed in a clinical trial.

Introduction

Osteoarthritis (OA) is the commonest form of arthritis and affects approximately 1 in 4 adults older than 45 years in age(1). There is a paucity of effective structure-modifying drug for OA, and, analgesics only have a modest effect size (ES) and may cause troublesome and potentially serious side-effects(2, 3). Consequently, many people undergo total joint replacement (TJR), most commonly at the knee or the hip. An estimated 1.9 million knee or hip TJRs are projected to be performed each year in the USA alone by the year 2030(4).

Our recent research demonstrated that β-adrenoreceptor blocking drugs (β-blockers) atenolol and propranolol have anti-nociceptive effects on knee and/or hip pain, with the largest ES for propranolol(5). Prior to this, we reported lower opioid consumption and less severe joint pain in people with large-joint lower limb OA prescribed β-blockers(6), and β-blocker prescription associated with lower opioid use at day 30 in another study on patients undergoing knee TJR(7). However, this was not confirmed in a study using Osteoarthritis Initiative (OAI) data(8). Whether β-blockers reduce incidence of TJR in people with OA is not known. In intervention studies, propranolol, a β-blocker drug, has analgesic benefit on musculoskeletal pain due to fibromyalgia and temporomandibular joint dysfunction and reduces post-operative analgesic requirement(24-26). It may be particularly suitable as an analgesic for OA with comorbid anxiety(28), neuropathic pain non-responsive to NSAIDs and driven by β_2 adrenoreceptor stimulation(18), and those with low catechol-O-methyltransferase (COMT) gene activity(29). The latter is of particular mechanistic relevance as >70% Caucasians have COMT (158Met) polymorphisms that confers low COMT gene activity(30).

Thus, the objective of this study was to examine whether β-blocker prescription associates with a lower risk of lower limb arthroplasty in a primary-care population with knee or hip OA.

Methods

Study Design: Cohort study.

Data source: Data from CPRD were used. Incepted in the year 1987, CPRD is a longitudinal anonymised electronic database containing health records of >10 million people in the UK(9). CPRD participants are representative of the UK population in terms of age, sex, and ethnicity(9).

Ethical approval: ISAC of the Medicines and Healthcare products Regulatory Authority (ISAC Reference: 18_227R).

Study population: Age ≥40 years, diagnosed with knee or hip OA between 1st January 1990 and 31st December 2013, at-least 2-year disease and exposure free prior registration in the CPRD before OA diagnosis, and contributing acceptable research quality data in up-to-standard GP practices (Appendix 1).

Exposure: New continuous β-blocker prescription, defined as ≥2 prescriptions of β-blockers within a 60-day period after the first OA diagnosis (new user design).

Unexposed: Participants without a prescription of β-blocker, or with a single β-blocker prescription after OA diagnosis date, matched to exposed participants for age at OA diagnosis (5-year age band), sex, OA location (knee or hip) and propensity score (PS) for β-blocker prescription (Appendix 1).

Start of follow-up (index date): Date of first β-blocker prescription for the exposed. The duration between OA diagnosis date and first β-blocker prescription date in the exposed was added to the OA diagnosis date of the matched unexposed to obtain their start of follow-up date. Thus, the exposed and matched unexposed participants had the same duration of OA prior to start of follow-up. This minimised any potential bias due to unequal disease duration prior to start of follow-up in exposed and unexposed participants as the risk of joint replacement increases with duration of OA(10). If this approach was not taken, exposed participants would

have had longer follow-up with OA prior to cohort entry (time taken to develop a comorbidity for which beta-blockers may be prescribed) and consequently be at higher risk of outcome.

Outcomes: [1] Knee or hip TJR (primary outcome), [2] knee TJR, and [3] hip TJR.

Exclusion criteria:

[1] Consultation for the below prior to start of follow-up:

- Conditions causing chronic pain: autoimmune inflammatory rheumatic diseases (rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, lupus, polymyalgia rheumatica); gout; radiculopathy; neuropathy; and fibromyalgia.
- Contra-indications for β-blockers: chronic obstructive pulmonary disease or asthma; peripheral vascular disease; heart block, aortic stenosis, and hypertrophic obstructive cardiomyopathy.

[2] Knee or hip TJR prior to or within 90 days of start of follow-up. Knee or hip TJR within 90 days after start of follow-up were excluded as we do not expect β-blockers to influence the rate of TJR immediately, and they may have been commenced during a pre-anaesthetic check-up.

End follow-up: Exposed participants were followed up from the index date. Participant follow-up ended at the earliest of date of first outcome, death date, transfer out date, date of last data collection, or study end (31/12/2018).

Ascertainment of exposure, outcomes and covariates: Read codes and product codes were used to ascertain these factors (Appendix 2).

Statistical Analyses: As participants prescribed β-adrenoreceptor blocking drugs are likely to have comorbidities, be older and have a high body mass index (BMI), a PS for β-blocker prescription was calculated using a cumulative logit regression model. Greedy nearest neighbour 1:1 matching, without replacement specifying a maximum calliper width of 0.001, was undertaken to match the exposed to unexposed participants. Missing values for BMI and smoking status were categorised as missing data for the purpose of PS matching as people with healthy lifestyle and normal BMI are more likely to have missing data in consultation-based databases such as CPRD where lifestyle and demographic factors are collected opportunistically(11). Mean, standard deviation (SD), n (%), and standardised mean difference (SMD) were used to examine the covariate balance between matched exposed and unexposed participants. Any variables that were in imbalance after PS matching were included in the model if the SMD was >0.10 as recommended(12).

Hazard ratios (HRs) and 95% confidence interval (CI) were calculated for each incident outcome (first Read code for the event) using a Cox proportional hazards model. Covariates that are likely to influence outcomes, e.g. progression of OA, or reflect health-seeking behaviour were included in the Cox model for additional confounder adjustment. These were:

- number of GP consultations for knee or hip injury, non-osteoporotic fractures (defined as fractures in any bone except the femur, distal radius, and vertebrae after the age of 18 years but before the age of 50

years in women and 60 years in men) prior to start of follow-up,
- number of analgesic prescriptions between the first consultation for knee/hip OA and start of follow-up,
- number of GP consultations, hospital out-patient referrals, hospital admissions in the 12-month period preceding start of follow-up,
- bisphosphonate or glucosamine/chondroitin sulphate prescription in the 12-month period prior to start of follow-up,
- new diagnosis of interphalangeal or thumb base OA, neck or back pain or spinal degenerative diseases after start of follow-up.

These analyses were stratified according to class of β-blocker drug used namely, β1 selective, intrinsic sympathomimetic activity, membrane stabilising effect, and lipophilic properties (low versus high). Number needed to treat (NNT) and 95% CI for a 2-year treatment duration were computed using the aHR and survival probability in control group as described previously(13).

Additionally, we performed multiple imputation to handle missing BMI values and smoking status using chained equations as a sensitivity analysis. Demographic factors, relevant diagnoses and prescriptions (Appendix 3), covariates that are likely to influence outcomes or reflect health-seeking behaviour listed above, primary outcome variable, and Nelson-Aalen estimator of baseline cumulative hazard were included in the imputation model as recommended(14). Ten imputed datasets were created to account for random variability(15). PS calculation, matching and Cox regression analyses were undertaken in each imputed dataset. However, we did not find substantial difference between the results with missing values as a dummy category and the imputed values (see Tables S1, S2, and S3 in the supplementary material). Thus, results are only reported with the missing category approach. Data management and analysis were performed in Stata MP v15.

Results

Data for 13,620 participants exposed to *β*-blockers and up to five age, sex and OA location matched unexposed participants (n = 48,636) were ascertained during the study period. Of these, data for 6,970 PS-matched *β*-blocker exposed (n = 3,485), and unexposed (n = 3,485) participants contributing 42,066 person-years of follow-up were analysed (Appendix 2). The majority of participants that had knee OA (81.12%), more than half our participants were women (57.89%) and the mean (SD) age at OA diagnosis was 65 (11) years. There was covariate balance between exposed and unexposed after PS-matching on all covariates except for hypertension (SMD = 0.115) for which there was minor imbalance (Table 1). Hypertension was included in the model as a covariate to account for the imbalance. After PS matching, unexposed participants had a similar number of consultations with their GP in the preceding 12-months as the exposed, with median (Inter Quartile Range) 11 (6 to 18) and 11 (7 to 18) GP visits, respectively.

Overall *β*-blocker prescription was not associated with hip or knee TJR (aHR 1.11; 95% CI 0.98–1.25), knee TJR (aHR 1.14; 95% CI 0.98 – 1.34) and hip TJR (aHR 1.23; 95% CI 0.96–1.57) (Table 2). Similar results were observed on the assessment of beta-blocker classes except for *β*-blocker with MSE which showed a reduction in the risk of knee or hip TJR (aHR 0.69; 95 % CI 0.52–0.93). The NNT (95%CI) to prevent joint replacement at

2 years follow-up was 32 (23–52). When data were stratified according to individual drugs, there was a protective effect for propranolol but an increase in the risk of knee or hip TJR for atenolol (Table 3; Fig. 1).

Discussion

This primary-care based PS-matched study reports that propranolol, a non-selective lipophilic β-blocker with a membrane stabilising effect and without intrinsic sympathomimetic activity, reduced risk of TJR. This accords with our previous study results where propranolol associated with reduced primary-care consultation for knee OA and knee pain, with reductions of 22% and 20%, respectively.

The analgesic effects of propranolol may be mediated by directly blocking the β_2 adrenoreceptors on the peripheral nociceptors, dorsal root ganglia, and superficial dorsal horn (16–18), or by indirect effects such as a reduction in the negative affective component of pain (19), regulation of the firing of periaqueductal grey neurons via gamma-Amino butyric acid (GABA)-mediated action, and interfering with the chronic sensitization processes in the rostral ventromedial medulla and locus coeruleus (20, 21). Additional mechanisms may include a potentiation of the analgesic effect of sub-therapeutic doses of opioids via dopaminergic and GABA receptor mediated pathways (22). Propranolol also induces infiltrative cutaneous analgesia by blocking the voltage sensitive Sodium (Na+) and Calcium (Ca2+) ion channels, reducing Na + and Calcium Ca2 + influxes, and decreasing intracellular cyclic adenosine monophosphate via reduction of adenyl cyclase activity (23) .

Our findings are broadly consistent with the results of some observational studies reporting less severe pain and lower analgesic requirements in people with OA prescribed β-blockers (6, 7). However, they do not accord with those of a study using data from the OAI which reported no difference in pain severity between people prescribed and not prescribed β-blockers. This may be due to a lack of power, with a modest sample size of 1,168 and only 15% of participants being exposed to β-blockers (27).

In the present study, atenolol prescription associated with an increased risk of TJR and this was an unexpected finding given the results of our previous study in which atenolol reduced the risk of incident knee pain. This discordance may be due to the fact that β_1-adrenoreceptor blockade reduces bone resorption and increases bone mineral density (31), and increased bone mineral density associates with an increased risk of TJR (32). Increased bone mineral density is also causally associated with end-stage OA according to a mendelian randomisation study using data from the UK biobank (33). Unlike β_1-adrenoreceptor blockade, β_2-adrenoreceptor blockade with propranolol does not affect bone resorption or increase bone mineral density (31).

The finding of this study needs to be confirmed in a randomised controlled trial and the safety of propranolol in this population needs to be demonstrated before propranolol may be adopted as an analgesic for OA. The NNT estimated from the present study is high. Strengths of the present study include a large sample size, balanced PS matched exposed and un-exposed groups, and adjustment for other covariates that reflect health-seeking behaviour or are recognised as potential risk factors for TJR in OA. GPs are the first port of call for people with chronic conditions in the UK, and it is extremely unlikely that someone with OA will be seen in a secondary care hospital service, including private settings, without consulting their GP first. Participants with less than two-year registration in the GP practice before the OA diagnosis date were excluded to reduce

the risk of prevalent cases being included as incident OA. We excluded participants with chronic painful conditions and contra-indications to β-blockers to minimise confounding by indication that may not be addressed by PS matching. We used a validated definition of primary care diagnosis of knee or hip OA to define the onset of follow-up period (34, 35) and did not define our population just on consultation for knee or hip joint pain. Similarly, we used a GP entry of joint replacement surgery to define our outcomes. This has been validated against Hospital Episode Statistics and UK joint registry data and shown to have excellent validity (36, 37). Only 60% of CPRD practices are linked to HES and restricting the dataset to such practices would result in loss of sample size.

However, there are several caveats to this study. Firstly, we used primary care diagnosis of knee or hip OA. This is likely to be later than the onset of symptoms. However, there is no reason to suspect that this delay will differ between exposed and unexposed individuals. The exposure status was based on prescription and not on actual drug taking. However, this will only bias the results towards a null effect. We dichotomised the exposure as present or absent. Further dose response analysis, examining the association between cumulative doses is warranted. We did not use individuals initiating another drug (i.e. active comparator) as controls because there is a hierarchy in the use of different drugs for the treatment of cardiovascular diseases in the UK driven by NICE guidelines. For instance, the NICE guidelines recommend beta-blockers to treat resistant hypertension that has failed to respond to most other anti-hypertensive agents including ACE inhibitors, angiotensin-II receptor blockers, diuretics and calcium channel blockers. On the contrary, they recommend beta-blockers as first-line drugs for treatment of atrial fibrillation, angina and heart failure. Thus, an active comparator study design, even when stratified according to the cardiovascular disease, would introduce greater bias. Primary-care prescriptions in the UK are typically issued for 4 weeks at a time. In this study, exposed participants were required to receive 2 prescriptions in a 60-day period in order to enrich the sample with participants likely to continue with β-blocker treatment. This potentially introduces immortal time bias as follow-up started with first prescription date. However, both exposed and unexposed participants were required to have at-least 90 days follow-up without TJR, immortal time bias does not affect the validity of our findings. Finally, despite our best efforts residual confounding by indication may remain.

Conclusion

In summary, we report that the non-selective β-blocker propranolol reduces the risk of knee or hip TJR. A randomised controlled trial is required to further evaluate the analgesic potential of propranolol in OA.

Abbreviations

OA: Osteoarthritis

TJR: Total joint replacement

COMT: Catechol-O-methyltransferase

UK: United Kingdom

ACE: Angiotensin-converting enzyme

NICE: The National Institute for Health and Care excellence

CPRD: Clinical Practice Research Datalink

HES: Hospital Episode Statistics

GP: General Practice

PS: Propensity score

NNT: Number Needed to Treat

OAI: Osteoarthritis Initiative

Na+: Sodium

Ca2+: Calcium

GABA: Gamma Aminobutyric Acid

aHR: adjusted Hazard Rate

SMD: Standard mean difference

SD: Standard deviation

BMI: body mass index

CI: Confidence Interval

ISAC: Independent Scientific Advisory Committee

ES: effect size

USA: United States of America

NSAIDS: Nonsteroidal anti-inflammatory drugs

Declarations

Ethical approval and Consent to participate.

Approval was obtained from ISAC of the Medicines and Healthcare products Regulatory Authority (ISAC Reference: 18_227R). As this is a database study, there was no contact with participants, hence it did not ascertain consent to participate.

Consent for publication

This manuscript used anonymised patient electronic health data from the CPRD.

Availability of supporting data.

This study used data from the CPRD. Due to the CPRD data sharing policy, we are unable to share this study's data. However, access to CPRD data can be directly sought from the CPRD.

Competing interest

This paper presents an independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit (RfPB) programme (grant reference number PB-PG-0816-20025). The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. AA has received departmental research grants from AstraZeneca, speaker bureau fees from Menarini, scientific meeting support from Pfizer, and author royalties from UpToDate, unrelated to this work. WZ has received honorarium from AstraZeneca and Grunenthal, and speaker fees from BioBarica, Regeneron and Hisun, unrelated to this work. Keele School of Medicine have received funding from Bristol Myers Squibb for advice provided by CMD on primary care recruitment to a non-pharmacological AF study. MD has received honoraria for attending ad hoc advisory boards on gout for Grunenthal and Mallinckrodt, and author royalties from UpToDate, and is an investigator in an AstraZeneca-funded, investigator-led, non-drug study (the 'Sons of Gout' study), unrelated to this work. The other authors have no conflict of interest to declare.

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Authors' contribution

All authors conceived the study, interpreted results, contributed to and approved the final version of the manuscript. GN performed data analysis supervised by AA and MJG. GN and AA wrote the first draft of the manuscript.

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Tables

Table 1
Covariate balance before and after propensity score matching

Covariates	Entire cohort			PS matched sample		
	Exposed (n = 4,641)	Unexposed (n = 9,118)	SMD	Exposed (n = 3,485)	Unexposed (n = 3,485)	SMD
Continuous covariates; mean (SD)						
Age at OA diagnosis	64.92 (11.18)	64.11 (11.18)	0.071	64.80 (11.16)	65.34 (11.49)	-0.048
Index of multiple deprivation in tertiles	5.86 (2.92)	5.94 (2.86)	-0.026	5.87 (2.89)	5.81 (2.87)	0.020
Duration of ischaemic heart disease/congestive cardiac failure*	1.21 (3.92)	0.83 (3.43)	0.101	1.12 (3.91)	1.28 (3.82)	-0.042
Duration of hypertension*	4.07 (6.97)	3.39 (6.51)	0.101	4.27 (7.34)	4.71 (6.26)	-0.065
Categorical covariates; n (%)						
Male	2,022 (43.57)	3,937 (43.18)	0.008	1,489 (42.73)	1,446 (41.49)	-0.025
Non-smoker	2,553 (55.01)	5,203 (57.06)	-0.009	1,985 (56.96)	2,005 (57.53)	-0.012
Current smoker	593 (12.78)	1,194 (13.09)	-0.041	430 (12.34)	391 (11.22)	0.035
Ex-smoker	1,239 (26.70)	2,218 (24.33)	0.054	900 (25.82)	910 (26.11)	-0.007
Smoking missing data	256 (5.52)	503 (5.52)	0.000	170 (4.88)	179 (5.14)	-0.012
Underweight	34 (0.73)	66 (0.72)	0.001	27 (0.77)	21 (0.60)	0.021
Normal weight	1,015 (21.87)	2,056 (22.55)	-0.016	762 (21.87)	732 (21.00)	0.021
Pre-obese	1,688 (36.37)	3,128 (34.31)	0.043	1,235 (35.44)	1,263 (36.24)	-0.017
Obese	1,375 (29.63)	2,710 (29.72)	-0.002	1,059 (30.39)	1,098 (31.51)	-0.024
BMI missing data	529 (11.40)	1,158 (12.70)	-0.040	402 (11.54)	371 (10.65)	0.028

SMD: Standardised mean difference * Duration in years of cardiovascular comorbidities prior to index date.

Covariates	Entire cohort			PS matched sample		
Hypertension	2,742 (59.08)	3,236 (35.49)	0.486	1,908 (54.75)	2,106 (60.43)	-0.115
Angina	473 (5.19)	672 (14.48)	0.316	373 (10.70)	344 (9.87)	0.027
Myocardial Infarction	494 (10.64)	251 (2.75)	0.320	240 (6.89)	192 (5.51)	0.057
Congestive cardiac failure	285 (6.14)	231 (2.53)	0.178	168 (4.82)	162 (4.65)	0.008
Atrial fibrillation	594 (12.80)	370 (4.06)	0.319	341 (9.78)	319 (9.15)	0.022
Stroke	305 (6.57)	496 (5.44)	0.048	232 (6.66)	254 (7.29)	-0.025
Chronic kidney disease	336 (7.24)	730 (8.01)	-0.029	266 (7.63)	298 (8.55)	-0.034
Diabetes	462 (9.95)	856 (9.39)	0.019	365 (10.42)	392 (11.25)	-0.027
Anxiety	675 (14.54)	1,063 (11.66)	0.085	479 (13.74)	518 (14.86)	-0.030
Migraine	335 (7.22)	498 (5.46)	0.072	247 (7.09)	265 (7.60)	-0.020
Tremor	133 (2.87)	133 (1.46)	0.097	92 (2.64)	96 (2.75)	-0.007
Osteoarthritis at any other joint	1,736 (37.41)	2,898 (31.78)	0.119	1,260 (36.15)	1,276 (36.61)	-0.010
Neck or back pain	1,984 (42.75)	3,626 (39.77)	0.061	1,475 (42.32)	1,508 (43.27)	-0.020
Calcium channel blockers	1,248 (26.89)	1,842 (20.20)	0.158	949 (27.23)	1,037 (29.76)	-0.056
ACE inhibitors/Angiotensin II receptor antagonists	1,577 (33.98)	2,207 (24.20)	0.217	1,162 (33.34)	1,269 (36.41)	-0.064
Bendroflumethiazide/Aldosterone antagonists/loop diuretics	2,294 (49.43)	2,875 (31.53)	0.371	1,616 (46.37)	1,748 (50.16)	-0.076
Alfa-adrenoreceptor blockers	270 (5.82)	378 (4.15)	0.077	211 (6.05)	214 (6.14)	-0.004
Aspirin/Clopidogrel	2,085 (44.93)	2,140 (23.47)	0.464	1,347 (38.65)	1,418 (40.69)	-0.042

SMD: Standardised mean difference * Duration in years of cardiovascular comorbidities prior to index date.

Covariates	Entire cohort			PS matched sample		
Statins/Fibrates	1,580 (34.04)	2,311 (25.35)	0.191	1,108 (31.79)	1,213 (34.81)	-0.064

SMD: Standardised mean difference * Duration in years of cardiovascular comorbidities prior to index date.

Table 2
The association between β-adrenoreceptor blocking drug prescription and knee or hip joint replacement

Outcomes	Exposed	Events	Person-time (years)	Event rate (95% CI)/ 1,000 person-years	Model 1 HR (95% CI)[1]	Model 2 HR (95% CI)[2]
Knee or hip replacement	No	459	17,637	26.02 (23.75–28.52)	1.00	1.00
	Yes	587	21,894	26.81 (24.73–29.07)	1.08 (0.96–1.22)	1.11 (0.98–1.25)
Knee replacement	No	278	14,730	18.87 (16.78–21.23)	1.00	1.00
	Yes	378	18,291	20.69 (18.69–22.86)	1.12 (0.96–1.31)	1.14 (0.98–1.34)
Hip replacement	No	119	2,782	42.77 (35.74–51.19)	1.00	1.00
	Yes	151	3,491	43.25 (36.88–50.73)	1.14 (0.90–1.45)	1.23 (0.96–1.57)

[1]PS matched. [2] As in model 1, and, additionally adjusted for number of GP consultations, hospital out-patient referrals, hospital admissions and number of bisphosphonate, glucosamine/chondroitin sulphate prescription in the 12 month period preceding index date; total number of GP consultations for knee or hip injury, non-osteoporotic fractures, hand osteoarthritis, neck or back pain or spinal degenerative diseases, hypertension, duration of OA prior to index date; number of analgesic prescription between the first consultation for knee/hip OA and beta-blocker prescription.

Table 3
The association between β-adrenoreceptor blocking drug prescription and knee or hip replacement: stratified according to drug class and drugs

Exposure status	Events (n)	Person-time (years)	Event rate per 1,000 person-years (95% CI)	Model 1 HR (95% CI)[2]	Model 2 HR (95% CI)[3]
Unexposed[1]	459	17,637	26.02 (23.75–28.52)	1.00	1.00
β-blocker class [≠]					
low lipophilic only	13	444	29.27 (17.00-50.41)	1.17 (0.67–2.03)	1.21 (0.69–2.13)
High lipophilic only	7	157	44.62 (21.27–93.60)	1.75 (0.83–3.69)	1.92 (0.91–4.08)
Beta1selective and low lipophilic	490	17,165	28.55 (26.13–31.19)	1.15 (1.01–1.30)	1.16 (1.02–1.32)
Beta1selective and high lipophilic	22	734	29.99 (19.75–45.55)	1.17 (0.77–1.80)	1.12 (0.73–1.73)
MSE and high lipophilic	55	3,327	16.53 (12.69–21.53)	0.67 (0.51–0.89)	0.69 (0.52–0.93)
β-blocker drug name					
Atenolol	371	12,929	28.70 (25.92–31.77)	1.19 (1.03–1.36)	1.17 (1.01–1.34)
Bisoprolol	116	4,174	27.79 (23.17–33.34)	1.04 (0.85–1.27)	1.17 (0.95–1.44)
Propranolol	53	3,193	16.60 (12.68–21.73)	0.68 (0.51–0.91)	0.71 (0.53–0.95)

[1]Comparison group is unexposed to β-blockers; [2]Propensity score matched; [3]As in model 1, and, additionally adjusted for number of GP consultations, hospital out-patient referrals, hospital admissions and number of bisphosphonate, glucosamine/chondroitin sulphate prescription in the 12 month period preceding index date; total number of GP consultations for knee or hip injury, non-osteoporotic fractures, hand osteoarthritis, neck or back pain or spinal degenerative diseases, hypertension, duration of OA prior to index date; number of analgesic prescription between the first consultation for knee/hip OA and beta-blocker prescription; [≠]β-blocker properties independent of each other; MSE: membrane stabilising effect. Drugs from the rest of β-blocker class combinations were not present.

Figures

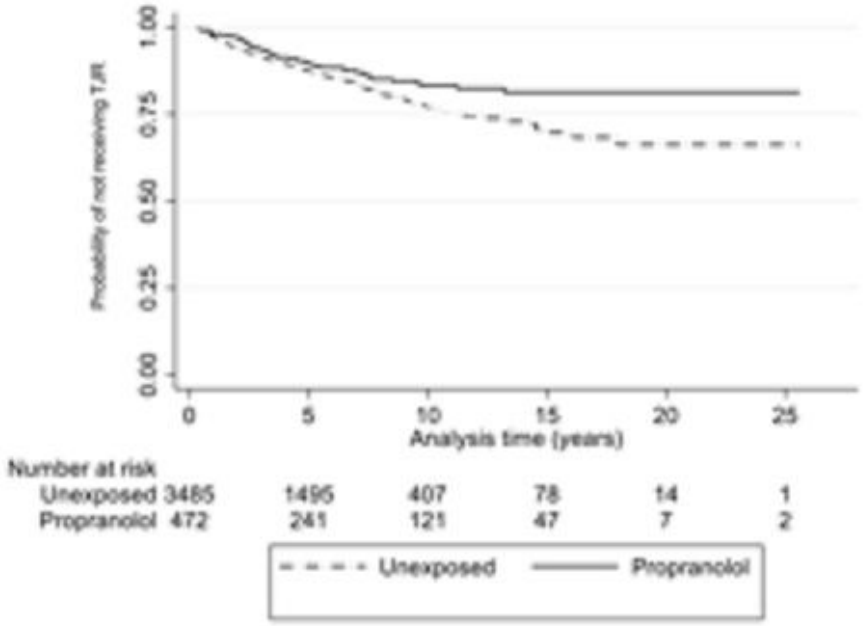

Figure 1

The association between propranolol and knee or hip replacement: Kaplan-Meier survival estimates

Supplementary Files

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- supplappendixTJR.docx