β-blocker prescription is associated with lower cumulative risk of knee osteoarthritis and knee pain consultations in primary care: a propensity score matched cohort study.

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Abstract

Objectives: To examine the association between β-blocker prescription and first primary-care consultation for knee osteoarthritis (OA), hip OA, knee pain and hip pain.

Methods: Data source: Clinical Practice Research Datalink. Participants aged ≥40 years in receipt of new oral β-blocker prescriptions were propensity score (PS) matched to an unexposed control. Cox proportional hazard ratios (HRs) and 95% confidence intervals (CI) were calculated, and adjusted for non-osteoporotic fractures, number of primary-care consultations for knee or hip injury, and, the number of primary-care consultations, out-patient referrals and hospitalizations in the 12-months preceding cohort entry. Analysis was stratified according to β-blocker class and for commonly prescribed drugs. P<0.05 was statistically significant.

Results: 111,718 β-blocker exposed participants were 1:1 PS matched to unexposed controls. β-blocker prescription was associated with reduced cumulative risk of knee OA, knee pain, and hip pain consultations with aHR(95%CI) 0.90(0.83–0.98); 0.88(0.83–0.92), and 0.85(0.79–0.90), respectively. Propranolol and atenolol were associated with a lower incidence of knee OA and knee pain consultations with aHRs between 0.78-0.91. *β*-blockers were associated with reduced incidence of consultation for large-joint lower-limb OA/pain as a composite outcome, defined as earliest of knee OA, knee pain, hip OA or hip pain consultation (aHR(95%CI) 0.87(0.84-0.90)).

Conclusion: Commonly used β-blockers have analgesic properties for musculoskeletal pain. Atenolol might be a therapeutic option for OA and cardiovascular co-morbidities in which β-blockers are indicated, while propranolol may be suitable for people with co-morbid anxiety. A confirmatory randomised controlled trial is needed before clinical practice is changed.

Keywords

Osteoarthritis

Pain

β-blockers

Anti-nociceptive

Comorbidity

Key messages

- In this large study, β-blockers reduced consultations for knee OA, and knee or hip pain.
- Atenolol could be considered for people with osteoarthritis and co-morbidities for which β-blockers are indicated.
- Propranolol may be a suitable analgesic for people with co-morbid anxiety.

Introduction

Osteoarthritis (OA) is the commonest form of arthritis and affects approximately half of all adults aged >50 years (1, 2). The pharmacologic management of OA is centred around optimising analgesia, but first-line drugs only have modest efficacy (3). Additionally, non-steroidal anti-inflammatory drugs (NSAIDs) may cause gastrointestinal, cardiovascular, and renal side-effects, particularly in the age groups affected by OA (4). People with OA are already at high risk of these adverse-events due to multi-morbidity (5, 6). Consequently, the use of opioids for OA pain has increased recently (7). However, opioids are poorly tolerated and may cause serious side-effects and dependency, and evidence for their efficacy in OA pain is limited (8, 9). Thus, there is an unmet need for developing a safe analgesic for OA.

Small uncontrolled studies suggest that *β*-adrenoreceptor blocking drugs (*β*-blockers) have anti-nociceptive effects in fibromyalgia, temporo-mandibular dysfunction, and migraine (10-12). Additionally, polymorphisms in the β_2-adrenoreceptor gene associates with chronic painful conditions (13-15). Recently, we reported a negative association between *β*-blocker prescription and severe knee pain and opioid prescription in adults with knee or hip OA awaiting total joint replacement (16). However, these results were not confirmed in another study (17), and, whether the analgesic effect is specific to a sub-class of *β*-blockers is not known.

Thus, the purpose of this study was to investigate the analgesic potential of *β*-blockers in a primary-care cohort. The specific objectives were to examine the association between *β*-blocker prescription and first primary-care consultation for knee OA (primary outcome), hip OA, knee pain and hip pain. Additionally, we explored the data

to identify the class of *β*-blockers, and specific drugs, that are most likely to have an analgesic effect.

Methods:

Study Design: Cohort study

Data source: The Clinical Practice Research Datalink (CPRD). CPRD is a longitudinal anonymised electronic database containing health records of >10 million people in the UK (18). CPRD participants are representative of the UK population in terms of age, sex, and ethnicity (18). It contains details of diagnoses, symptoms and signs, and referral details stored as Read code and, records of primary-care prescriptions stored as drug names.

Ethical approval: ISAC of the MHRA (Reference: 18_227R).

Study population: CPRD registered participants aged ≥40 years, contributing data in general practice surgeries that met the data quality standards of CPRD between 1st January 1990 and 31st December 2017. This age cut-off was chosen as both the probability of exposure and outcome is low in the under 40s.

Exposure: First ever continuous *β*-blocker prescription, defined as ≥2 prescription for any oral *β*-blocker within a 60-day period. In the UK, primary-care prescriptions are usually issued every 4 weeks. We selected participants with ≥2 prescriptions within 60-days to exclude those who experience side-effects and discontinue treatment shortly after it was commenced.

Unexposed: Participants without prescription of *β*-blockers.

It is common to choose active comparators in pharmacoepidemiology studies. We did not use active comparator controls because there is a hierarchy in the use of drugs for the treatment of cardiovascular diseases driven by NICE guidelines in the UK. For

instance, NICE recommend *β*-blockers for resistant hypertension that has failed to respond to other anti-hypertensive agents. In contrast, they recommended *β*-blockers first line for atrial fibrillation, angina and heart failure. Thus, an active comparator study would introduce greater bias by comparing people with different severity of cardiovascular illnesses.

Propensity Score (PS) matching: As participants prescribed *β*-blockers are likely to have comorbidities and be older, a PS for *β*-blocker prescription was calculated and 1:1 matching undertaken to ensure unexposed and exposed participants were otherwise comparable. The PS included:

[1] demographic factors: age, sex, current smoker (yes, no), general practice surgery level index of multiple deprivation score.

[2] comorbidities: overweight or obese (body mass index (BMI) ≥25 kg/m^2) hypertension, angina, myocardial infarction, heart failure, atrial fibrillation, stroke, chronic kidney disease, diabetes, anxiety, migraine, and duration in years of each cardiovascular comorbidity prior to cohort entry; and

[3] prescriptions: calcium channel blockers, ACE inhibitors, angiotensin II receptor antagonists, bendroflumethiazide, aldosterone antagonists, loop diuretics, alfa-adrenoreceptor blocking drugs, aspirin, clopidogrel, statins, fibrates.

Outcomes: Primary-care consultation for knee OA, hip OA, knee pain, and hip pain (Table S2: Codelist). A primary-care diagnosis of OA at either the knee, hip or hands has a positive predictive value of 79.8%-82% in validation studies in the CPRD and similar primary-care databases (19, 20).

Index date: Date of the first of two consecutive prescriptions in the exposed (new user design). Unexposed participants were assigned the index date of their matched exposed participant.

Exclusion criteria: Consultation for any of the following prior to the index date:

- OA at any joint
- Knee, hip, neck or back pain
- Autoimmune inflammatory rheumatic diseases, or gout
- Radiculopathy, or neuropathy
- Fibromyalgia
- Contra-indications to *β*-blockers: asthma, chronic obstructive pulmonary disease, peripheral vascular disease, heart block, aortic stenosis, hypertrophic obstructive cardiomyopathy
- Two prescriptions for opioids, NSAIDs, gabapentin, pregabalin, duloxetine or amitriptyline in any 60-day period prior to the index date.
- Additionally, participants with <2 years of registration data before index date were excluded to reduce the chance of prevalent conditions (e.g. long-standing OA or pain) being considered as incident outcomes.

It is typical to require one-year disease free registration as entry criteria in studies using consultation-based databases. However, people with OA may not consult their GP in a given 12-month period. Thus, a disease-free registration of 2-years prior to cohort entry was chosen in consultation with the GP-expert in the team to minimises the chance of prevalent OA cases being classified as incident outcome(s).

Follow-up: Exposed and unexposed participants were followed-up from index date until the earliest of outcome of interest, death date, transfer out date, date of last data collection, study end date (31/12/2017), or date of last prescription of *β*-blockers plus 28 days (typical duration of primary-care prescriptions in UK) in the exposed, and an assigned pseudo-end date for the unexposed participant using the end-date of their

matched exposed person. The follow-up period of participants not experiencing an outcome was censored. Given the well-known effects of propranolol on pain sensitivity (21), we anticipated *β*-blockers to have an analgesic effect in the short term and follow-up period >28 days after the date of last *β*-blocker prescription was disregarded from primary analysis *a priori*. In a secondary analysis, we extended the follow-up period to earliest of outcome of interest, death date, transfer out date, date of last data collection, and study end date (31/12/2017).

Statistical Analysis The PS 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. Participants with missing data on smoking and BMI were classified as non-smoker and normal BMI respectively. This approach was chosen due to >50% missing data on these variables, and because they are missing not at random in consultation-based databases such as CPRD (22-25). Mean, standard deviation (SD), n (%), and standardised difference (d) were used to examine the covariate balance between exposed and unexposed participants. If d was more than +0.10 or less than -0.10, the variable was included in the model as a covariate as per Nguyen *et al* (26).

Cox proportional hazard ratios (HRs) and 95% confidence interval (CI) were calculated for each outcome after checking that proportional hazard assumptions were met using log-log plots and a formal test to assess departure from proportional hazards (Figure S1). Nelson-Aalen graphs were plotted. Covariates likely to influence outcomes but are not related to exposure (i.e. number of GP consultations for knee or hip injury, and non-osteoporotic fractures prior to the index date) or which reflect general health-seeking behaviour and may influence consultation for musculoskeletal pain (i.e. number of GP consultations, out-patient hospital referrals, and hospital admissions in

the 12-month period preceding cohort entry) were included in the model. Non-osteoporotic fractures were included as a surrogate of knee or hip injury. They were defined in this study as fractures between the ages of 19-49 years in women, and 19-59 years in men respectively. Vertebral, femoral and distal radius fractures were excluded as these are target sites for osteoporotic fractures.

The analyses were stratified according to the class of *β*-blocker used, namely β_1 selective or non-selective, intrinsic sympathomimetic activity (ISA) present or absent, membrane stabilising effect (MSE) present or absent, and high or low lipophilic properties; and commonly prescribed *β*-blocker drugs. Robustness of results were assessed using first of OA or pain consultation at the knee or hip as an outcome.

Sensitivity analysis: Given the extent of missing data on smoking status and BMI, a complete-case analysis was performed. In this, exposed and unexposed participants with missing data were excluded, 1:1 PS matching was performed and the analysis adjusted for the a priori selected covariates listed above. Data management and analysis were performed using Stata(v15). Statistical significance was considered at $p<0.05$.

Results

Data for 223,436 1:1 PS-matched *β*-blocker exposed (n=111,718) and unexposed (n=111,718) participants were included (Figure S2). The mean (SD) follow-up period while receiving *β*-blocker prescription and total follow-up period, including when not prescribed *β*-blockers was 2.75 (4.03) and 11.29 (6.59) years respectively in the exposed. The corresponding follow-up for the unexposed participants was 2.35 (3.17) and 10.02 (6.38) years respectively. There was covariate balance after PS-matching on all variables except for age for which there was imbalance (d =-0.147, Table S1).

Age was included in the model to account for the imbalance. After PS matching, unexposed and unexposed participants had similar number of primary-care consultations in the preceding 12-months, with mean (SD) 5.27 (7.05) and 5.81 (6.92) visits, respectively, d = 0.08.

β-blocker prescription was associated with reduced cumulative risk of incident primary-care consultation for knee OA (aHR(95%CI) 0.90(0.83–0.98)), knee pain (aHR(95%CI) 0.88(0.83 – 0.92)) and hip pain (aHR(95%CI) 0.85(0.79 – 0.90)) (Table 1, Figure 1). On secondary analysis, there was no association between *β*-blocker prescription and primary-care consultation for knee OA or hip OA when the follow-up period extended beyond the end of *β*-blocker prescription, while there was an increased incidence of primary-care consultation for knee pain or hip pain (Table 2).

Of the *β*-blocker classes that could be assessed, high lipophilic non-selective *β*-blockers were associated with lower cumulative incidence of primary-care consultation for knee OA and knee pain with aHR(95%CI) of 0.78(0.63-0.95) and 0.80(0.72-0.89) respectively (Table 3). Similarly, low lipophilic, β_1-selective drugs without MSE or ISA reduced the cumulative incidence of primary-care consultation for knee pain (aHR(95%CI) 0.88(0.80-0.93)) and knee OA (aHR(95%CI) 0.92(0.84-1.01)). Additionally, lipophilic β_1-selective and low-lipophilic non-selective *β*-blockers, without MSE or ISA, were associated with a reduced cumulative incidence of primary-care consultation for knee pain with aHR(95%CI) 0.81(0.66-1.00)), and 0.85(0.71-1.02), respectively. There was a trend for similar effects when hip OA and hip pain consultations were the outcomes of interest (Table 3; Figure S3). When data were stratified according to individual drugs, there was a significant protective effect for propranolol and atenolol for knee OA and knee pain consultations and, for atenolol for hip pain consultations (Table 4, Figure 2). There was a trend for propranolol

prescription to associate with a lower cumulative risk of hip pain consultation (Table 4; Figures S4).

β-blockers were associated with reduced cumulative risk of primary-care consultation for large-joint lower-limb OA and/or pain, defined as the earliest of knee OA, knee pain, hip OA or hip pain (aHR(95%CI) 0.87(0.84-0.90)). The aHR (95%CI) was 0.80 (0.73-0.87) for propranolol, and 0.85 (0.82-0.89) for atenolol. On complete case PS-matched analysis all covariates were balanced. Exposure to *β*-blockers was associated with lower cumulative incidence of primary-care consultation for knee OA (aHR (95%CI) 0.85(0.76-0.96)), knee pain (0.77(0.72-0.82)), hip pain (0.70(0.64-0.76)) and hip OA(0.85(0.72-1.02)), adjusted for the *a priori* selected covariates.

Discussion

This primary-care based study reports that *β*-blocker prescription was associated with reduced primary-care consultation for knee OA, knee pain, and hip pain. Interestingly, the effect disappeared after the end of *β*-blocker prescription, and participants had more consultations for knee and hip pain in this period. This suggests that the effect of *β*-blockers may potentially be due to analgesia rather than structure-modification. However, we did not assess the latter in this study.

The greatest effect size was observed for propranolol, a non-selective lipophilic *β*-blocker with MSE. Analgesic effects of propranolol have been reported. In a randomised double-blind placebo-controlled crossover study (n=40), propranolol significantly lowered pain scores due to temporomandibular dysfunction (27). Similar findings were observed in fibromyalgia and temporomandibular dysfunction in controlled studies shortly after low-dose intravenous propranolol (0.1 mg/kg) (10). Propranolol also reduces post-operative analgesic requirement (28). However, an

analgesic effect for propranolol was not demonstrated in people with extensive burns and in other experimental models of pain (29, 30). Propranolol is used in the treatment of anxiety, and 21% of OA patients have comorbid anxiety (31) making it particularly attractive in this scenario.

The β_1 adrenoreceptor selective drug atenolol was associated with reduced cumulative risk of primary-care consultation for knee OA, knee pain and hip pain. Identical in properties to atenolol, esmolol, also has an analgesic effect (32). It reduces both intraoperative (Standard Mean Difference (SMD) (95%CI) -1.60(-2.25 to -0.96)) and post-anaesthesia opioid consumption (SMD (95%CI) -1.21(-1.66 to -0.77)) (32). Atenolol is used for the treatment of cardiovascular conditions such as angina, hypertension and supraventricular tachycardia, and our findings suggest that it might be suitable for the treatment of cardiovascular comorbidities in symptomatic OA patients. However, confirmation of our findings in a randomised controlled trial (RCT) is needed before practice is changed.

The analgesic effect of β-blockers is mediated by β_2 adrenoreceptor blockade. β_2 adrenoreceptors are present on peripheral nociceptors, dorsal root ganglia and superficial dorsal horn, and their stimulation results in hyperalgesia that is blocked by either non-selective or β_2 adrenoreceptor selective drugs (33-35), but not by indomethacin (35). The analgesic effect of β-blockers does not seem to be mediated by the β_1 adrenoreceptor. For example, the hyperalgesic state in low catechol-O-methyl transferase gene activity is blocked by propranolol but not by selective β_1-adrenoreceptor blockers (36). Non-selective β-blockers reduce the negative affective component of pain (37), regulate the firing of periaqueductal grey neurons via a GABA-mediated action, and interfere with the chronic sensitization processes in the rostral ventromedial medulla and locus coeruleus (38, 39). Thus, the analgesic effect of

atenolol is likely to be mediated by its β_2 adrenoreceptor blocking activity. Although classified as β_1 selective, its β_1/β_2 adrenoreceptor selectivity is relatively modest at 4.7(40).

This study suggests that β_1-adrenoreceptor selective drugs may also have an analgesic effect. This is consistent with the findings of a previous cross-sectional study (16), and that of another study using data from people undergoing total knee arthroplasty (41). In the latter study, β-blocker prescription was associated with lower opioid use at day 30 (aOR(95%CI) 0.89(0.80-0.99)) (41). Ninety percent of participants in this study were prescribed β_1-adrenoreceptor selective drugs (41). However, the findings of these studies are not consistent with those of a study using data from the Osteoarthritis Initiative (17). That study reported comparable pain score, proportion reporting widespread pain, and opioid consumption in people with knee OA prescribed β-blockers and other anti-hypertensive medications (17). However, that was a hospital-based study with a different comparator i.e. “prescription of another anti-hypertensive drug”, had a relatively modest sample size (n=1168), and only 15% participants were prescribed β-blockers resulting in potential type-2 error (17).

Strengths of this study include a large sample size, balanced PS matched exposed and un-exposed groups, and adjustment for covariates that reflect health seeking behaviour, or are risk factors for OA. GPs are the first physician option for people with chronic conditions in the UK, and it is extremely unlikely that someone with OA will be seen in a hospital service, including in private settings, for the first time, without ever consulting their GP. Only GPs refer patients to NHS hospitals for long-term conditions. Participants with less than two year registration in the general practice surgery before the index date were excluded to reduce the chance of prevalent cases being classified as incident outcomes. Finally, 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.

However, there are several caveats. Firstly, we could not undertake multiple imputation to account for missing smoking status and BMI data because these were missing in 50.5% and 60.3% participants respectively, and multiple imputation is not recommended with such degree of missingness (22, 23). In addition, smoking and BMI are not missing at random in consultation-based databases, therefore multiple imputation should not be used (24, 25). Secondly, CPRD participants with missing data are likely to be healthier. After PS matching there was a comparable proportion of people in exposed and unexposed groups with missing data on BMI and smoking minimising any potential for confounding. Thirdly, we used GP diagnosis of OA to define our primary outcome. Although this has been validated previously (19, 20), its' PPV for OA diagnosis is c. 80% and some participants may not be diagnosed, limiting the validity of our findings. We used primary care consultations to define the outcomes. This is later than the onset of symptoms as most patients defer seeing their GP for chronic musculoskeletal pain. However, there is no reason to suspect that this delay will differ between the groups. Similarly, access to GP surgery and ability to pay for repeat prescription may also affect the results. This is likely to play a small role as healthcare is free at the point of delivery in the NHS and socio-economically disadvantaged patients are eligible for free NHS prescriptions. Furthermore, we did not examine the association between *β*-blocker prescription and total joint replacement in this study as the mean follow-up was short. Finally, we only dichotomised the exposure as two or more than two prescriptions within 60 days. Further dose response analysis, examining the association between cumulative dose and number of prescriptions are warranted.

In summary, both non-selective and selective *β*-blockers may reduce the cumulative risk of incident OA. Atenolol might be a consideration for people with OA and cardiovascular co-morbidities, while propranolol may be suitable in people with OA and anxiety. However, a RCT is necessary to further evaluate these possibilities before clinical practice is changed.

Contributorship AA and AV conceptualised the study. AA, AV, MJG, MAM, CM, NT, WZ and MD planned the study. AA, MJG, GN, NT, WZ, MAM, CM, AV and MD developed the analysis plan. GN carried out the data management and analysis. AA and GN wrote the first manuscript draft. MJG, MAM, GN, NT, WZ, CM, AV and MD reviewed the manuscript critically and approved the final version.

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investigator-led, non-drug study (the ‘Sons of Gout’ study), unrelated to this work. The other authors have no conflict of interest to declare.

Data availability statement: This study used data from the Clinical Research Datalink (CPRD). Due to the CPRD data sharing policy, data used in this study cannot be shared with the third party. However, access to CPRD data can be requested directly from the CPRD.

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Figure legends

Figure 1: Cumulative hazard of (A) knee osteoarthritis and (B) knee pain consultation in β-blocker exposed and unexposed participants. Data restricted to the last prescription of β-blocker.

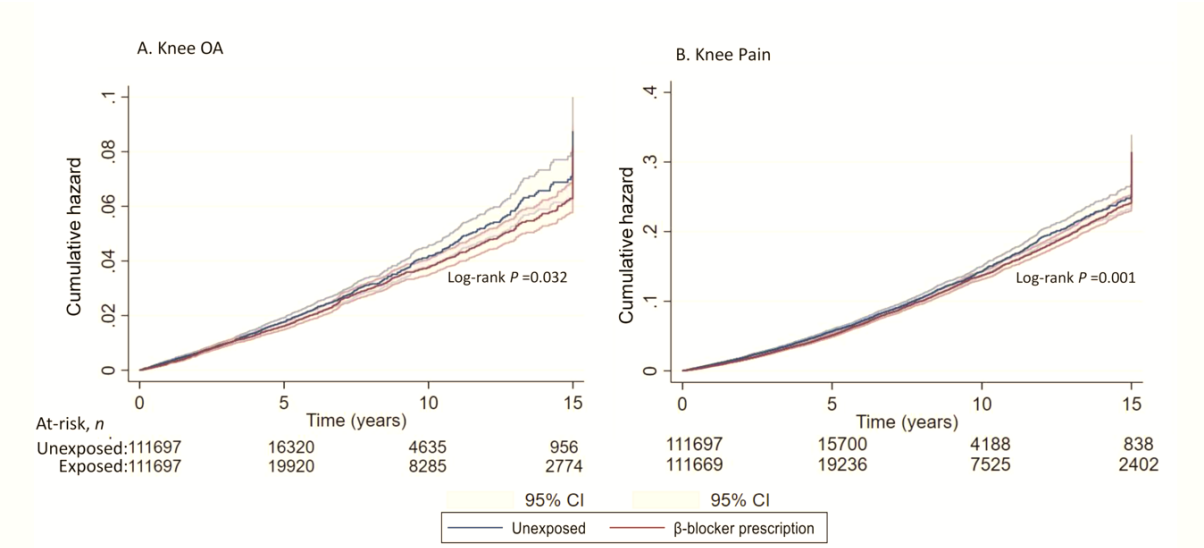

Figure 1: Cumulative hazard plots with 95% CIs of [A] knee osteoarthritis (OA) and [B] knee pain consultation in β-blocker exposed and unexposed participants. Data restricted to the last prescription of β-blocker, censored at 15 years of follow-up. The log-rank test was used to estimate the difference in cumulative hazards.

Figure 2: Cumulative hazard of (A) knee osteoarthritis and (B) knee pain consultation in atenolol and propranolol exposed and unexposed participants. Data restricted to the last prescription of β-blocker.

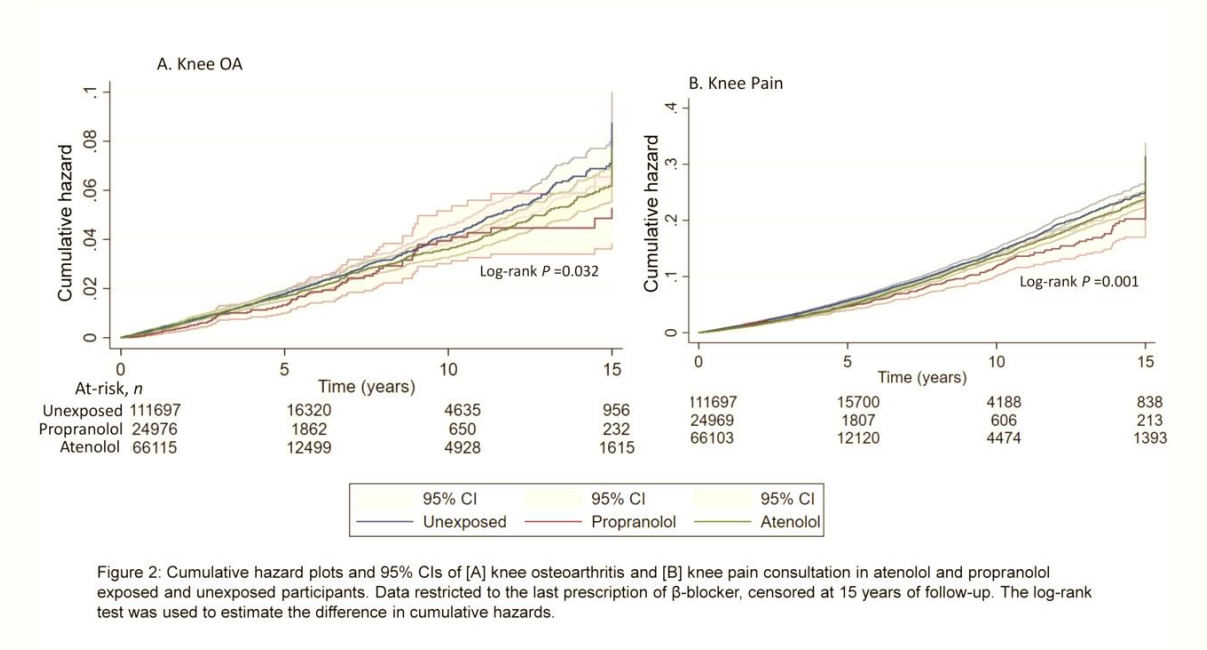

Figure 2: Cumulative hazard plots and 95% CIs of [A] knee osteoarthritis and [B] knee pain consultation in atenolol and propranolol exposed and unexposed participants. Data restricted to the last prescription of β-blocker, censored at 15 years of follow-up. The log-rank test was used to estimate the difference in cumulative hazards.

Table 1: The association between β-blocker prescription and primary-care consultation for incident osteoarthritis and joint pain: follow-up period restricted to end of β-blocker prescription (n=223,436)

Outcomes	**Exposed**	**Events (n)**	**Person-time (years)**	**Event rate (95% CI)/ 1,000 person-years**	**PS matched HR (95% CI)**	**PS matched and adjusted HR (95% CI)[1]**
Knee osteoarthritis	No	986	262,003	3.76 (3.54 – 4.01)	1.00	1.00
	Yes	1,101	307,231	3.58 (3.38 – 3.80)	0.90 (0.83 – 0.99)	0.90 (0.83 – 0.98)
Hip osteoarthritis	No	451	263,753	1.71 (1.56– 1.87)	1.00	1.00
	Yes	530	310,045	1.71 (1.57 – 1.86)	0.94 (0.83 – 1.06)	0.94 (0.83 – 1.07)
Knee pain	No	3,074	255,003	12.06 (11.64 – 12.49)	1.00	1.00
	Yes	3,560	297,027	11.99 (11.60 – 12.37)	0.91 (0.87 – 0.96)	0.88 (0.83 – 0.92)
Hip pain	No	1,767	259,515	6.81 (6.50 – 7.13)	1.00	1.00
	Yes	1,981	304,454	6.51 (6.23 - 6.80)	0.87 (0.82 – 0.93)	0.85 (0.79 – 0.90)

[1]adjusted for age, number of GP consultations, hospital out-patient referrals, hospital admissions in the 12-month period preceding cohort entry, total number of GP consultations for knee or hip injury prior to cohort entry and non-osteoporotic fractures.

Table 2: The association between β-blocker prescription and primary-care consultation for incident osteoarthritis and joint pain: follow-up period not restricted to end of β-blocker prescription (n=223,436).

Outcomes	Exposed	Events	Person-time (years)	Event rate (95% CI)/ 1,000 person-years	PS matched HR (95% CI)	PS matched and adjusted HR (95% CI)[1]
Knee osteoarthritis	No	4,809	1,118,936	4.30 (4.12-4.42)	1.00	1.00
	Yes	5,330	1,261,516	4.23 (4.11-4.34)	0.96 (0.92-1.00)	0.97 (0.93-1.01)
Hip osteoarthritis	No	2,253	1,137,529	1.98 (1.90-2.06)	1.00	1.00
	Yes	2,512	1,282,641	1.96 (1.88-2.04)	0.96 (0.91-1.02)	0.98 (0.93-1.04)
Knee pain	No	15,921	1,049,982	15.16 (14.93-15.40)	1.00	1.00
	Yes	19,473	1,168,291	16.67 (16.44-16.90)	1.07 (1.05-1.09)	1.03 (1.01-1.05)
Hip pain	No	9,392	1,095,747	8.57 (8.40-8.75)	1.00	1.00
	Yes	11,532	1,225,992	9.41 (9.24-9.58)	1.06 (1.03-1.09)	1.04 (1.02-1.07)

[1] adjusted for age, number of GP consultations, hospital out-patient referrals, hospital admissions in the 12 month period preceding cohort entry, total number of GP consultations for knee or hip injury prior to cohort entry and non-osteoporotic fractures.

Table 3: The association between β-blocker prescription and incident osteoarthritis and pain: stratified according to drug class

	Knee osteoarthritis					Knee pain			
β-blocker class[≠]	**Events (n)**	**Person-time (years)**	**Event rate 95% CI/ 1,000 p-yr**	**PS matched and adjusted[2] HR 95% CI**		**Events (n)**	**Person-time (years)**	**Event rate 95% CI/ 1,000 p-yr**	**PS matched and adjusted HR[2] 95% CI**
Unexposed[1]	986	262,003	3.76 (3.54-4.01)	1		3,074	255,003	12.06 (11.64-12.49)	1
Non-selective, low lipophilic	39	10,462	3.73 (2.72-5.10)	0.84 (0.60-1.17)		124	10,127	12.24 (10.27-14.60)	0.85 (0.71-1.02)
Non-selective, high lipophilic, MSE	101	38,419	2.63 (2.16-3.20)	0.78 (0.63-0.95)		392	37,508	10.45 (9.47-11.54)	0.80 (0.72-0.89)
β1selective, low lipophilic	900	240,757	3.74 (3.50-4.00)	0.92 (0.84-1.01)		2,860	232,271	12.31 (11.87-12.77)	0.88 (0.83-0.93)
β1selective, high lipophilic	33	8,635	3.82 (2.72-5.38)	0.95 (0.67-1.35)		88	8,370	10.51 (8.53-12.96)	0.81 (0.66-1.00)
	Hip osteoarthritis					**Hip pain**			
Unexposed[1]	451	263,753	1.71 (1.56-1.88)	1		1767	259,515	6.81 (6.50-7.13)	1
Non-selective, low lipophilic	15	10,567	1.42 (0.86-2.35)	0.74 (0.44-1.23)		73	10,345	7.06 (5.61-8.88)	0.84 (0.67-1.07)
Non-selective, high lipophilic, MSE	46	38,600	1.19 (0.89-1.59)	0.79 (0.58-1.07)		216	38,035	5.68 (4.97-6.49)	0.88 (0.76-1.01)
β1selective, low lipophilic	433	243,134	1.78 (1.62-1.96)	0.96 (0.84-1.10)		1557	238,680	6.53 (6.22-6.86)	0.83 (0.77-0.89)
β1selective, high lipophilic	20	8,678	2.30 (1.49-3.57)	1.26 (0.80-1.97)		68	8,498	8.00 (6.31-10.15)	1.07 (0.84-1.36)

[1]Comparison group is unexposed to β-blockers; [≠]β-blocker properties [2]Propensity score matched and adjusted for age, number of GP consultations, hospital out-patient referrals, hospital admissions in the 12 month period preceding cohort entry, total number of GP consultations for knee or hip injury prior to cohort entry and non-osteoporotic fractures; ISE: Intrinsic sympathomimetic effect; MSE: membrane stabilising effect. Drugs from the rest of β-blocker class combinations are not used in clinical practice. Lipophilic non-selective β-blockers, lipophilic non-selective β-blockers with ISE and MSE, low-lipophilic non-selective β-blockers with ISE and MSE, low lipophilic β1-selecive blockers with ISE and MSE were excluded as the number of outcome events were fewer than fifty for both knee pain and knee OA.

Table 4: The association between commonly prescribed β-adrenoreceptor blocking drugs and incident osteoarthritis and pain

	Knee osteoarthritis				Knee pain			
β-blocker	**Event**	**Person-time (years)**	**Event rate (95% CI)/ 1,000 person-year**	**PS matched and adjusted[2] HR 95% CI**	**Event**	**Person-time (years)**	**Event rate (95% CI)/ 1,000 person-year**	**PS matched and adjusted HR[2] 95% CI**
Unexposed[1]	986	262,003	3.76 (3.54-4.01)	1	3,074	255,003	12.06 (11.64-12.49)	1
Atenolol	686	191,455	3.58 (3.32-3.86)	0.91 (0.82-1.00)	2138	185,636	11.52 (11.04-12.02)	0.86 (0.81-0.91)
Propranolol	93	35,663	2.61 (2.13-3.20)	0.78 (0.63-0.97)	342	34,948	9.79 (8.80-10.88)	0.78 (0.69-0.87)
Bisoprolol	204	47,037	4.34 (3.78-4.98)	0.99 (0.85-1.16)	695	44,469	15.63 (14.51-16.84)	0.98 (0.91-1.08)
Sotalol	38	10,328	3.68 (2.68-5.06)	0.81 (0.58-1.14)	124	9,990	12.41 (10.41-14.80)	0.88 (0.73-1.05)
Metoprolol	33	8,635	3.82 (2.72-5.38)	0.96 (0.67-1.35)	88	8,370	10.51 (8.53-12.96)	0.82 (0.66-1.01)
	Hip osteoarthritis				**Hip pain**			
Unexposed[1]	451	263,753	1.71 (1.56-1.88)	1	1,767	259,515	6.81 (6.50-7.13)	1
Atenolol	327	193,111	1.69 (1.52-1.89)	0.94 (0.81-1.08)	1,153	190,067	6.07 (5.73-6.43)	0.80 (0.74-0.86)
Propranolol	43	35,833	1.20 (0.89-1.62)	0.81 (0.59-1.11)	195	35,348	5.52 (4.79-6.35)	0.89 (0.76-1.03)
Bisoprolol	99	47,733	2.07 (1.70-2.53)	1.02 (0.82-1.28)	386	46,380	8.32 (7.53-9.20)	0.92 (0.82-1.03)
Sotalol	14	10,432	1.34 (0.79-2.27)	0.71 (0.42-1.21)	72	10,210	7.05 (5.60-8.88)	0.85 (0.67-1.08)
Metoprolol	20	8,678	2.30 (1.49-3.57)	1.26 (0.81-1.98)	68	8,498	8.00 (6.31-10.15)	1.07 (0.84-1.36)

[1]Comparison group is unexposed to β-blockers; [2]Propensity score matched and adjusted for age, number of GP consultations, hospital out-patient referrals, hospital admissions in the 12 month period preceding cohort entry, total number of GP consultations for knee or hip injury prior to cohort entry and non-osteoporotic fractures; *Restricted to drugs with ten or more outcome events.