Updated Review of Gout Management
Dr Gareth S Tarr - 28th May 2016

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WINELANDS
Rheumatology Centre | Medical Research Centre
‘The Gout’ by James Gillray (1799)
Epidemiology

- Commonest inflammatory arthritis in men;
  - Increasing frequency in females.
- 7% of men over the age of 65;
- 3% of women aged over 85 years;
- Strongly related to:
  - Metabolic syndrome,
  - Chronic renal impairment,
  - Certain drug treatments, including diuretics.

Several epidemiological studies have demonstrated an increase in the severity and prevalence of gout.

Why, then,
despite the possibility of early and accurate diagnosis,
the availability of effective treatment and our insight
into the severity and consequences of the disease,
is gout managed so ineffectively?
Gout: why is this curable disease so seldom cured?

Michael Doherty, Tim L Jansen, George Nuki, Eliseo Pascual, Fernando Perez-Ruiz, Leonardo Punzi, Alexander K So, Thomas Bardin
Progression of Joint Damage
Common Misconceptions

- Self-limited disease
- Crystal deposition continues despite long ‘symptom’ free period → Destructive Arthritis.
- Benign, rather than serious
- Humorous.
- Historically – “Disease of kings”.

Rates of adherence and persistence with allopurinol therapy among gout patients in Israel

Gisele Zandman-Goddard¹,²,.*, Howard Amital²,³,.*, Nadya Shamrayevsky², Raanan Raz²,⁴, Varda Shalev²,⁴ and Gabriel Chodick²,⁴

Results. A total of 7644 patients were identified. Among men, the incidence of gout was strongly associated with age, ranging from 0.5 per 1000 among adults younger than 45 years to more than 36 per 1000 among elderly men aged 85 or older. A total of 1331 gout patients (17% of the study population) were adherent to allopurinol therapy, 36% and 47% had partial and poor adherence, respectively. Persistence analysis indicated that the average duration until therapy was discontinued was similar among men (358 days) and women (379 days). Women aged 45–64 years, non-married individuals, those of low socioeconomic status and those with lower body weight were more likely to discontinue therapy. Logistic regression (n = 2471, 32% of the study sample) showed a 4.5 risk of non-compliance among 45- to 65-year-old women. Better compliance was achieved among those with comorbidities, particularly among patients with concomitant cardiovascular disease.

Conclusion. Only one out of six gout patients is adherent with allopurinol. Intervention programmes to increase adherence with treatment should focus on high-risk populations.
These distorted perceptions of the nature of gout have a marked negative effect on patients’ attitudes to their gout and its treatment.

‘Punch Cures the Gout, the Colic and the “tisick”’ by James Gillray (1799)
What about the Doctor’s approach?

- Gout is largely managed by general practitioners.
- Majority of patients are never referred for a specialist opinion.
- Approach to gout management is beset with misconceptions and myths.
Primary care providers’ knowledge, beliefs and treatment practices for gout: results of a physician questionnaire

Leslie R. Harrold¹, Kathleen M. Mazor², Amarie Negron¹, Jessica Ogarek², Cassandra Fimeno² and Robert A. Yood³

Abstract

Objective. We sought to examine primary care providers’ gout knowledge and reported treatment patterns in comparison with current treatment recommendations.

Methods. We conducted a national survey of a random sample of US primary care physicians to assess their treatment of acute, intercritical and tophaceous gout using published European and American gout treatment recommendations and guidelines as a gold standard.

Results. There were 638 respondents (response rate of 41%), most of whom worked in private practice (63%) with >16 years experience (52%). Inappropriate dosing of medications in the setting of renal disease and lack of prophylaxis when initiating urate-lowering therapy (ULT) accounted for much of the lack of compliance with treatment recommendations. Specifically for acute podagra, 53% reported avoidance of anti-inflammatory drugs in the setting of renal insufficiency, use of colchicine at a dose of ≤2.4 mg/day and no initiation of a ULT during an acute attack. For intercritical gout in the setting of renal disease, 3% would provide care consistent with the recommendations, including initiating a ULT at the appropriate dose with dosing titration to a serum urate level of ≤6 mg/dl and providing prophylaxis. For tophaceous gout, 17% reported care consistent with the recommendations, including ULT use with dosing titration to a serum urate level of ≤6 mg/dl and prophylaxis.

Conclusion. Only half of primary care providers reported optimal treatment practices for the management of acute gout and <20% for intercritical or tophaceous gout, suggesting that care deficiencies are common.
Management Questions

- When do I start Urate lowering therapy (ULT)?
- Do I continue ULT during an acute attack?
- What is the role of colchicine?
- How long do I continue colchicine for?
- What level of serum uric acid am I aiming for?
Management of Acute Gouty Attack

Mild-moderate pain, particularly for an attack affecting only 1 or a few small joints, or 1-2 large joints.

Assess the Severity

Monotherapy

NSAID (e.g. Arcoxia)

Systemic Steroids

Colchicine

Option: Initial Combination Therapy

Severe Pain, Polyarticular attack, multiple large joints.
Etoricoxib Pharmacokinetics: Absorption and $t_{1/2}^*$

$Etoricoxib$ Pharmacokinetics: Absorption and $t_{1/2}^*$

$t_{1/2} = \text{half-life}$

*Single oral doses to healthy subjects

<table>
<thead>
<tr>
<th>Drug</th>
<th>$T_{\text{max}}$ (hour)</th>
<th>$t_{1/2}$ (hour)</th>
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<tbody>
<tr>
<td>Etoricoxib</td>
<td>1</td>
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<tr>
<td>Celecoxib</td>
<td>2–3</td>
<td>8–12</td>
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<tr>
<td>Diclofenac</td>
<td>1–5.25</td>
<td>2</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>0.75–1.5</td>
<td>2</td>
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<td>Meloxicam</td>
<td>4–5</td>
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<tr>
<td>Naproxen</td>
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<td>12–17</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>2</td>
<td>4.5</td>
</tr>
<tr>
<td>Nimesulide</td>
<td>2–3</td>
<td>2–5</td>
</tr>
</tbody>
</table>

$T_{\text{max}} = \text{time to maximum plasma concentration}$
Etoricoxib vs. Naproxen or Ibuprofen
Endoscopy Studies: Gastro-duodenal Ulcers

Although the studies were not designed to compare ulcer rates of placebo with etoricoxib, subsequent analysis revealed significant differences in Study 1 (p=0.002) and Study 2 (p=0.003).\textsuperscript{2,3}

\textsuperscript{a}Cumulative incidence rate of gastroduodenal ulcers $\geq$3 mm at week 12. Cumulative incidence rate from life-table analysis may not equal number of events/$n \times 100$; \textsuperscript{b}p<0.001 for etoricoxib and placebo vs. naproxen; \textsuperscript{c}p<0.001 for placebo vs. ibuprofen; \textsuperscript{d}p=0.007 for etoricoxib vs. ibuprofen;

\textsuperscript{5}500 mg twice daily; \textsuperscript{6}800 mg three times daily

Hunt RH et al \textit{Aliment Pharmacol Ther} 2003;17:201–210;
Etoricoxib vs. Nonselective NSAIDs: GI PUBs

Etoricoxib had lower incidence of confirmed PUBs in the clinical development program*

\[ \text{Etoricoxib} \geq 60 \text{ mg (n=3142)} \]
\[ \text{Nonselective NSAIDs combined}^{**} \text{ (n=1828)} \]

\[ p<0.001 \]

\[ \sim 55\% \text{ Risk reduction} \]

NSAIDs = nonsteroidal anti-inflammatory drugs; PUBs = perforations, ulcers, bleeds

*Combined analysis of 10 clinical trials in OA, RA, and chronic low back pain; **Naproxen 1000 mg/day, ibuprofen 2400 mg/day, or diclofenac 150 mg/day

<table>
<thead>
<tr>
<th>Drug</th>
<th>No. of patients</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indomethacin vs. phenylbutazone</td>
<td>28</td>
<td>1973</td>
</tr>
<tr>
<td>Proquazone vs. indomethacin</td>
<td>18</td>
<td>1978</td>
</tr>
<tr>
<td>Sulindac vs. phenylbutazone</td>
<td>47</td>
<td>1979</td>
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<tr>
<td>Fenoprofen vs. phenylbutazone</td>
<td>30</td>
<td>1979</td>
</tr>
<tr>
<td>Feprazone vs. phenylbutazone</td>
<td>24</td>
<td>1980</td>
</tr>
<tr>
<td>Meclofenamate vs. indomethacin</td>
<td>20</td>
<td>1983</td>
</tr>
<tr>
<td>Flurbiprofen vs. phenylbutazone</td>
<td>33</td>
<td>1985</td>
</tr>
<tr>
<td>Flurbiprofen vs. indomethacin</td>
<td>29</td>
<td>1986</td>
</tr>
<tr>
<td>Indomethacin + allopurinol vs. azapropazone</td>
<td>93</td>
<td>1987</td>
</tr>
<tr>
<td>Tenoxicam</td>
<td>10</td>
<td>1987</td>
</tr>
<tr>
<td>Colchicine vs. placebo</td>
<td>43</td>
<td>1987</td>
</tr>
<tr>
<td>Ketoprofen vs. indomethacin</td>
<td>59</td>
<td>1988</td>
</tr>
<tr>
<td>Etodolac vs. naproxen</td>
<td>60</td>
<td>1990</td>
</tr>
<tr>
<td>Etodolac vs. naproxen</td>
<td>61</td>
<td>1991</td>
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<tr>
<td><strong>Etoricoxib vs. indomethacin</strong></td>
<td><strong>150</strong></td>
<td><strong>2002</strong></td>
</tr>
<tr>
<td><strong>Etoricoxib vs. indomethacin</strong></td>
<td><strong>189</strong></td>
<td><strong>2004</strong></td>
</tr>
</tbody>
</table>

*List includes only double-blind clinical studies of oral agents based on extensive English-language Medline literature search (drug names and gout as search terms; no limit on year of publication; accessed January 2004). All published double-blind clinical studies may not be included.
Cardiovascular risk??
Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

Coxib and traditional NSAID Trialists' (CNT) Collaboration*

Summary

Background The vascular and gastrointestinal effects of non-steroidal anti-inflammatory drugs (NSAIDs), including selective COX-2 inhibitors (coxibs) and traditional non-steroidal anti-inflammatory drugs (NSAIDs), are not well characterised, particularly in patients at increased risk of vascular disease. We aimed to provide such information through meta-analyses of randomised trials.

Methods We undertook meta-analyses of 280 trials of NSAIDs versus placebo (124,513 participants, 68,342 person-years) and 474 trials of one NSAID versus another NSAID (229,296 participants, 165,456 person-years). The main outcomes were major vascular events (non-fatal myocardial infarction, non-fatal stroke, or vascular death); major coronary events (non-fatal myocardial infarction or coronary death); stroke; mortality; heart failure; and upper gastrointestinal complications (perforation, obstruction, or bleed).

Findings Major vascular events were increased by about a third by a coxib (rate ratio [RR] 1.37, 95% CI 1.14–1.66; p=0.0009) or diclofenac (1.41, 1.12–1.78; p=0.0036), chiefly due to an increase in major coronary events (coxibs 1.76, 1.31–2.37; p=0.0001; diclofenac 1.70, 1.19–2.41; p=0.0032). Ibuprofen also significantly increased major coronary events (2.22, 1.10–4.48; p=0.0253), but not major vascular events (1.44, 0.89–2.33). Compared with placebo, of 1000 patients allocated to a coxib or diclofenac for a year, three more had major vascular events, one of which was fatal. Naproxen did not significantly increase major vascular events (0.93, 0.69–1.27). Vascular death was increased significantly by coxibs (1.58, 99% CI 1.00–2.49; p=0.0103) and diclofenac (1.65, 0.95–2.85, p=0.0187), non-significantly by ibuprofen (1.90, 0.56–6.41; p=0.17), but not by naproxen (1.08, 0.48–2.47, p=0.80). The proportional effects on major vascular events were independent of baseline characteristics, including vascular risk. Heart failure risk was roughly doubled by all NSAIDs. All NSAID regimens increased upper gastrointestinal complications (coxibs 1.81, 1.17–2.81, p=0.0070; diclofenac 1.89, 1.16–3.09, p=0.0106; ibuprofen 3.97, 2.22–7.10, p<0.0001; and naproxen 4.22, 2.71–6.56, p<0.0001).

Interpretation The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the size of these risks can be predicted, which could help guide clinical decision making.
Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials

• Meta-analysis
• 280 trials
• 124513 patients
• 68342 patient years
• ibuprofen = diclofenac = coxibs
• Naproxen associated less vascular events.

Interpretation: The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the size of these risks can be predicted, which could help guide clinical decision making.
Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials.

Coxib and traditional NSAID Trials Initiative.


Original Article

Nonsteroidal Anti-Inflammatory Drugs and Cardiovascular Outcomes in Women

Results From the Women’s Health Initiative

Anthony A. Bavry, MD, MPH; Fridtjof Thomas, PhD; Matthew Allison, MD; Karen C. Johnson, MD; Barbara V. Howard, PhD; Mark Hlatky, MD; JoAnn E. Manson, MD, DrPH; Marian C. Limacher, MD


The vascular risks of high-dose diclofenac, and possibly ibuprofen, are comparable to coxibs, whereas high-dose naproxen is associated with less vascular risk than other NSAIDs. Although NSAIDs increase vascular and gastrointestinal risks, the size of these risks can be predicted, which could help guide clinical decision making.

Evaluation of the Efficacy of Etoricoxib in Ankylosing Spondylitis

Results of a Fifty-Two-Week, Randomized, Controlled Study

Désirée van der Heijde,¹ Herbert S. B. Baraf,² Cesar Ramos-Remus,³ Andrei Calin,⁴ Arthur L. Weaver,⁵ Michael Schiff,⁶ Margaret James,⁷ Jan E. Markind,⁷ Alise S. Reicin,⁷ Agustin Melian,⁷ and Maxime Dougados⁸
Increased mortality in ankylosing spondylitis is related to disease activity

Gunnstein Bakland,¹ Jan Tore Gran,² Johannes C Nossent¹

- Continuous NSAIDs for 30 years
- Overall mortality risk 14.2% (Cardiovascular disease = 40%).
- BUT
- Continuous NSAIDs reduced CVS mortality.

Ann Rheum Dis 2011; 70 (11) : 1921
Celestone IAS vs. IMI

- Highly fat soluble
- Cross all cell membranes rapidly.
- Systemically available within a few minutes after injection.
- You don’t have to inject locally.
- Intra-muscular (IM) injections are also very effective.
- Benefit of a local injection is mainly ‘duration of symptom relief’.
Inadequate Response

- ≤20% improvement in pain score within 24 hours
- < 50% at > 24 hours

Consider an alternative diagnosis

Switch to alternative Monotherapy

Option: Add on combination therapy.

Treatment Outcome?

Treatment Outcome?
Experimental Drugs for an Acute Attack

- Therapies targeting IL-1b blockage are currently being investigated.

- These include:
  - Anakinra (an IL-1 receptor antagonist),
  - Rilonacept (a soluble receptor-Fc fusion protein that engages and inhibits both IL-1α and IL-1β)
  - Canakinumab (a fully human monoclonal anti-IL-1β antibody).

2012 American College of Rheumatology Guidelines for Management of Gout. Part 1: Systematic Nonpharmacologic and Pharmacologic Therapeutic Approaches to Hyperuricemia

DINESH KHANNA, JOHN D. FITZGERALD, PUJA P. KHANNA, SANGMEE BAE, MANJIT K. SINGH, TUHINA NEOGI, MICHAEL H. PILLINGER, JOAN MERILL, SUSAN LEE, SHRADDHA PRAKASH, MARIAN KALDAS, MANEESH GOGIA, FERNANDO PEREZ-RUIZ, WILL TAYLOR, FRÉDÉRIC LIOTÉ, HYON CHOI, JASVINDER A. SINGH, NICOLA DALBETH, SANFORD KAPLAN, Vandana Niyyar, DANIELLE JONES, STEVEN A. YAROWS, BLAKE ROESSLER, GAIL KERR, CHARLES KING, GERALD LEVY, DANIEL E. FURST, N. LAWRENCE EDWARDS, BRIAN MANDELL, H. RALPH SCHUMACHER, MARK ROBBINS, NEIL WENGER, and ROBERT TERKELTAUB
Establish the Diagnosis

Baseline recommendations for Patients with Gout
- Patient education, with the initiation of diet, lifestyle changes.
- Secondary causes of hyperuricaemia
- Prescription medications that can exacerbate hyperuricaemia
- Evaluate disease burden.

Indications for Urate Lowering Therapy
- Tophus or tophi
- > 2 attacks per year
- CKD stage 2 or worse
- Past urolithiasis
**TREAT TO TARGET URIC ACID LEVEL**

1st Line Xanthine Oxidase Inhibitor
- Allopurinol
- Febuxostat

Alternative 1st Line therapy
- Probenecid

Acute Gout prophylaxis
- Colchicine 0.5 mg BD
- NSAID (e.g., Arcoxia)

Uric acid ≤ 0.35 mmol/L

Allopurinol

- Dose adjusted for serum uric acid
- Begin a 100mg daily, and titrate upwards
- Max dose 900mg daily (in divided doses)
- Renal impairment: begin with 50mg daily

A  Risk allele of ABCG2

Extra-renal underexcretion

Renal overloading effect due to extra-renal underexcretion

Extra-renal excretion

Renal excretion

Increased UUE and FE_{UA} (= increased renal excretion)

Predisposing to ROL type gout

Urate synthesis inhibitor

B  Risk allele of SLC2A9

Renal underexcretion

Extra-renal excretion

Renal excretion

Decreased UUE and FE_{UA}

Predisposing to RUE type gout

Uricosuric agents

TREAT TO TARGET achieved

YES
- Continue acute gout prophylaxis
- Regularly monitor uric acid level

NO
- Duration of gout prophylaxis
- Big Problem?

- Ongoing gout symptoms
- >1 Tophus present
- No tophi initially – 3 months
- Tophi initially – 6 months

Big Problem?

Long-term treatment with either colchicine or NSAIDs.
Therapeutic options for Chronic Gout

Big Problem?

Pegloticase

Uricosuric Agents

Lesinurad

Arhalofenate

Ulodesine

Levotofitospam
Reversal of chronic refractory tophaceous gout with erosions with pegloticase

Progression of Gout

Asymptomatic Hyperuricaemia -> Acute Attack -> Recurrent attacks -> Chronic Gout -> Uric acid nephrolithiasis -> Chronic Nephropathy

What can asymptomatic hyperuricaemia and systemic inflammation in the absence of gout tell us?

Is uric acid a biomarker or does it have a pathophysiological role in driving systemic inflammation?

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>Relative Risk of Hypertension</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hawaii–Los Angeles–Hiroshima, 2001</td>
<td>140 men</td>
<td>2.0 times greater at 15 yr (high vs. low quartile)</td>
</tr>
<tr>
<td>Osaka Factory, 2003</td>
<td>433 men</td>
<td>1.0 mg/dl, increased 27 mm Hg SBP at 5 yr</td>
</tr>
<tr>
<td>Osaka Health Survey, 2003</td>
<td>2310 men</td>
<td>1.13 times greater per SD increment at 6 yr</td>
</tr>
<tr>
<td>Okinawa, 2004</td>
<td>4489 men</td>
<td>1.46 times greater for men (uric acid ≥7 mg/dl) and 1.94 for women (uric acid ≥6 mg/dl) at 13yr</td>
</tr>
<tr>
<td>Framingham Heart, 2005</td>
<td>3329 adults</td>
<td>1.17 times greater per SD increment at 4 yr</td>
</tr>
<tr>
<td>Normative Aging, 2006</td>
<td>2062 men</td>
<td>125 times greater at 21 yr (uric acid &gt;6.5 mg/dl)</td>
</tr>
<tr>
<td>ARIC, 2006</td>
<td>9104 adults</td>
<td>1.1 times greater per SD increment at 9 yr</td>
</tr>
<tr>
<td>Beaver Dam Health Survey, 2006</td>
<td>2520 adults</td>
<td>1.65 times greater at 10 yr (high vs. low quintile)</td>
</tr>
<tr>
<td>MRFIT, 2007</td>
<td>3073 men</td>
<td>1.1 times greater per SD increment at 6 yr</td>
</tr>
</tbody>
</table>
Impact of allopurinol use on urate concentration and cardiovascular outcome

Li Wei,¹ Isla S. Mackenzie,¹ Yang Chen,² Allan D. Struthers³ & Thomas M. MacDonald¹
Use of allopurinol may be associated with an approximately 20% decreased risk of first-ever non-lethal MI.

Our study did not confirm that MI risk was reduced in colchicine.
Gout, although correlated with uric acid and cardiovascular disease, was **independently associated** with total and cardiovascular mortality.

**Mortality** impact of gout increased with rising uric acid Concentrations.
Gout as a risk factor for myocardial infarction and stroke in England: evidence from record linkage studies

Olena O. Seminog and Michael J. Goldacre

Results. The risk of MI and stroke was elevated, and similar, in both datasets. In the all-England dataset, which included 202,033 hospital patients with gout, the RR for MI following gout was 1.82 (95% CI 1.78, 1.85), for all stroke 1.71 (1.68, 1.75), ischaemic stroke 1.68 (1.64, 1.73), haemorrhagic stroke 1.69 (1.61, 1.77) and stroke of unspecified type 2.00 (1.95, 2.06). Associations were stronger in younger than older age groups, and in the younger were stronger in women than men.

Conclusion. Gout was associated with increased risk of stroke as well as MI. These findings should be considered by clinicians and may have implications for preventive management of circulatory disease risks in people with gout.
Association of uric acid and carotid artery disease in patients with ischemic stroke

E. Kumral¹, B. Karaman¹, M. Orman², C. Kabaroglu³

and size of plaques. Conclusion – Our study demonstrated that higher uric acid level is strongly associated with CAD. Elevated uric acid might be injurious for large cerebral arteries with some probable confounding risk factors. Further prospective large clinical trials will determine whether lowering uric acid level reduces the frequency of CAD and ischemic stroke.
Systematic Review and Meta-Analysis of Methotrexate Use and Risk of Cardiovascular Disease

Renata Micha, RD, PhDᵃ,⁎, Fumiaki Imamura, PhDᵃ, Moritz Wyler von Ballmoos, MD, PhDᵇ, Daniel H. Solomon, MDᶜ, Miguel A. Hernán, MD, DrPHᵃ,e, Paul M. Ridker, MDᵈ, and Dariush Mozaffarian, MD, DrPHᵃ,d

• 18% reduced risk of Myocardial Infarction
• 21% reduced risk for total Cardio-vascular disease

Conclusion, methotrexate use is associated with a lower risk for CVD in patients with chronic inflammation. These findings suggest that a direct treatment of inflammation may reduce CVD risk.
How low is too low?

Gout and the risk of Alzheimer’s disease: a population-based, BMI-matched cohort study

Na Lu,¹,² Maureen Dubreuil,¹,³ Yuqing Zhang,¹ Tuhina Neogi,¹ Sharan K Rai,⁴ Alberto Ascherio,⁵ Miguel A Hernán,⁵ Hyon K Choi²

The End – Thank you