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Mortality in patients with gout treated with allopurinol: a systematic review and meta-analysis

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Abstract

Background: Urate-lowering therapy (predominantly allopurinol) is highly effective as a treatment for gout, but its wider long-term effects remain unclear. This systematic review and meta-analysis aimed to ascertain the association between allopurinol use in patients with gout and mortality.

Method: MEDLINE, EMBASE, CINAHL and the Cochrane Library were searched from inception to August 2018. Articles eligible for inclusion used a cohort design and examined cardiovascular or all-cause mortality in patients diagnosed with gout and prescribed allopurinol. Information on study characteristics, design, sample size and mortality risk estimates were extracted. Article quality was assessed using the Newcastle-Ottawa Scale. Included articles were described in a narrative synthesis and (where possible) risk estimate data were pooled.

Results: Four articles reported a hazard ratio (HR) risk estimate for all-cause mortality in patients with gout using allopurinol, two of these also reported cardiovascular mortality. Two articles found allopurinol to be protective in patients with gout, one found no statistically significant association and one found no statistically significant effect of escalation of allopurinol dosage on all-cause or cardiovascular-related mortality. Data pooling was possible for all-cause mortality and found no association between allopurinol use in patients with gout and all-cause mortality compared to patients with gout not using allopurinol (adjusted HR 0.80 (95%CI (0.60, 1.05).

Conclusions: There was no significant association between all-cause mortality and allopurinol use in people with gout. However, the number of included studies was small, suggesting that further studies are needed.

Significance and Innovations

- We found no significant association between all-cause mortality and allopurinol use in people with gout.

- Further studies taking into account allopurinol dose and achievement of target serum urate levels are required.

Introduction

Gout is the most common inflammatory arthritis, affecting 2.5% of UK adults (1). Its pathogenesis is well understood: elevation of serum urate levels above 360µmol/L (6mg/DL) can lead to formation and deposition of monosodium urate crystals in joints and soft tissues that can result in agonisingly painful acute flares of joint inflammation (2). Without treatment, flare frequency increases, chronic joint damage occurs and mobility/function reduce, resulting in impaired health-related quality of life (3). There is also an increased risk of serious comorbidities (e.g. cardiovascular disease) and premature mortality (4, 5).

Treating gout should be straightforward due to the availability of safe, effective long-term treatment to lower urate levels (urate-lowering therapy (ULT)), allowing dissolution of existing urate crystals and preventing new crystal formation, leading to the cessation of gout flares (6, 7). International guidelines recommend ULT is offered to all patients with gout and initiated upon confirmation of diagnosis, once any current flare has abated (8, 9). Allopurinol is the first-line ULT and should be initiated at a low-dose (100mg or less, daily), followed by up-titration in 100mg increments until urate levels are suppressed below 360µmol/L (6mg/DL). Despite clear guidelines and benefits, only 30% of patients are prescribed allopurinol and, of those, only 40% have treatment escalated to achieve the target serum urate level of <360µmol/L, suggesting that many patients with gout could receive better ULT (10).

In addition to its success in treating gout, other benefits of allopurinol have been suggested in patients with kidney and cardiovascular diseases. It has been shown to be associated with decreased likelihood of renal events (initiation of dialysis, doubling serum creatinine, ≥50% decrease in estimated glomerular filtration rate) in two-thirds of patients with chronic kidney disease (11). Improvements in cardiovascular function include increased peripheral blood-flow due to improved endothelial function in patients with chronic heart failure (12). However, despite these improvements in morbidity, it remains unclear whether the benefits of allopurinol extend to reducing premature mortality in patients with gout. In patients with hyperuricaemia (the precursor to gout), use of allopurinol has been estimated to be

associated with a 25% lower risk of mortality during follow-up compared with untreated patients (13, 14).

Despite guidelines recommending earlier prescription of ULT (8, 9) and the reported benefits on comorbidities, the use of allopurinol to treat gout remains sub-optimal. Though the reasons behind this are multifaceted, one contributing factor relates to the apprehension of patients and clinicians to initiate life-long treatment without a clear understanding of the long-term effects (1). As the overall balance of potential benefit and risk in the role of allopurinol on mortality in patients with gout remains unclear, this systematic review and meta-analysis examined the association between the use of allopurinol in patients with gout and cardiovascular or all-cause mortality.

Materials and Methods

A systematic review of research literature was conducted. Medical literature databases were searched to identify articles which included patients with gout treated using allopurinol and had reported the risk of cardiovascular or all-cause mortality in their sample. Meta-analysis was used to determine pooled risk estimates of mortality. The protocol for this systematic review and meta-analysis was registered on PROSPERO (ID CRD42017056011) and the systematic review was undertaken following PRISMA guidelines.

Data sources, searches and study selection

Four electronic bibliometric databases were searched for articles (Embase, Medline, CINAHL and Cochrane Studies). These were required to fulfil the following eligibility criteria: i) study sample was formed from adults with a diagnosis of gout, ii) use of allopurinol to treat gout, iii) reporting of risk estimates of all-cause or cardiovascular mortality and iv) study used a cohort design. Cohort studies were targeted specifically as their populations are more likely than RCTs to be representative of the general population and normal courses of treatment, therefore increasing the likelihood that this systematic review and meta-analysis produces a generalisable result. Case-control and cross-sectional studies were excluded as they would not describe outcomes over time. No restrictions were imposed on the time periods for publication, with medical literature databases searched to inception to August 2018. There

were no language restrictions; however, if translational facilities were not available for an article, they were excluded.

Data extraction

Data were extracted by two authors (CAH, JAP) with the main data including; demographic information (age, sex, country of origin etc), study sample size, numbers of patients with gout, study setting (e.g. primary care), exposures (e.g. allopurinol), mortality outcome (e.g. all-cause, cardiovascular), definition of gout and method of adjusted risk estimates regarding the association between gout treated with allopurinol and cardiovascular and all-cause mortality risk estimates.

Quality Assessment

All articles finally included in the systematic review were quality appraised independently by two assessors (CAH, JAP). Any disagreement on initial scoring was discussed, and if this could not be agreed upon, the decision was arbitrated by a third reviewer (ER). Methodological quality was assessed using the Newcastle-Ottawa Scale (NOS) for cohort studies (15).

Meta-analysis

Where a sufficient number of articles (≥3) were identified, a random-effects meta-analysis was used to pool reported mortality risk estimates along with their 95% confidence interval (CI). Heterogeneity was assessed by I^2. The meta-analysis was undertaken in STATA (version 14).

Results

Literature Search

From 362 articles identified by the initial literature search, 90 duplicates were removed. The titles of the remaining 272 articles were screened, after which 37 articles remained. After an abstract review of these, 32 articles were excluded. The full text of the remaining 5 articles were reviewed in full and a final four articles were deemed to fulfil the inclusion criteria (**Figure 1**).

Sample characteristics

Four articles examined all-cause mortality (16-19) and two of these (16, 19) also examined cardiovascular mortality in the same population. Of the articles included in the review, one study population was from Taiwan, one was from the USA and the other two were from the United Kingdom (UK). All four articles estimated risk of mortality using hazard ratios (HR) (16-19) (**Table 1**).

The Taiwanese study by Chen et al (16) sourced its cohort from the medical insurance data from MJ Health Screening centres, which contained 49,460 individuals over the age of 17 who had consultations since 1996. Gout was defined using ICD-9 codes identified between 1997 and 2002. Kuo et al. (18) used a UK primary care data source, the Clinical Practice Research Datalink (CPRD), and defined incident gout by Read codes between 1995 and 1999. Dubreuil et al. (17) used a different UK primary care data source (The Health Improvement Network (THIN)), defining gout by Read codes between January 2000 to May 2010. The study by Coburn et al. (19) sourced its cohort from the US Department of Veterans Affairs Health Administration (VHA) between 2001 and 2008 and defined gout by its ICD-9 definition. Unlike the previous three studies, Coburn et al. focused specifically on the effect on risk of all-cause and cardiovascular mortality of increasing allopurinol dosage in patients.

All articles were cohort studies and used matching based on propensity scores. Chen et al and Dubreuil et al followed up their patients from exposure onwards (date of diagnosis for Chen et al and initiation of allopurinol for Dubreuil et al). Kuo et al and Coburn et al both utilised landmark analysis to avoid immortal time bias. Kuo et al only included patients who were alive by the landmark time-points (one year and three years); this method excludes the

initial time-period immediately after gout diagnosis, reducing the possibility of conferring an unfair survival advantage on the allopurinol treated group. Coburn et al. used two models; in model 1, they followed up patients from exposure, and in model 2, they followed up patients after a 2-year landmark.

Quality Assessment

All four articles included representative patients with gout, assessed exposures and outcomes using secure methods (medical records) and employed appropriate methods to compare subjects, with and without gout, to avoid confounding by indication affecting the veracity of results, with all four studies employing propensity score matching. Three of the four papers also employed methods to attempt to negate immortal time bias; Chen et al. used time-index matching between patients and controls and Coburn et al. utilised an analytical method which involved only following up patients alive two years after allopurinol initiation. Kuo et al. employed a landmark analysis method which only followed up patients alive after one-year post-allopurinol initiation and then three years after initiation. Loss-to-follow-up was minimal and accounted for in analyses.

Risk of all-cause mortality

Chen et al. and Dubreuil et al. both found allopurinol to have a protective effect on all-cause mortality in patients with gout. Chen et al. reported an adjusted hazard ratio (HR) of 0.39 (95% CI 0.22-0.70) (allopurinol was slightly more protective against all-cause mortality than the use of any ULT medication (0.47 (0.29-0.79)), and Dubreuil et al. reported an adjusted HR of 0.81 (0.70-0.92). However, Kuo et al found no association between the use of allopurinol in patients with gout and all-cause mortality, with a HR of 0.99 (0.87-1.12) for 1-year landmark analysis and 1.01 (0.92-1.09) for the 3-year landmark analysis, the latter of which was included in the pooled analysis. Finally, Coburn et al. reported a HR for all-cause mortality in patients with gout for whom allopurinol dosage was increased, compared with patients with gout using a constant dose. They reported a significant increase in all-cause mortality for model 1 (propensity score matching, 1.08 (95% CI 1.01–1.17)) and a non-

significant HR for model 2 (inclusion of 2-year landmark analysis, 1.05 (95% CI 0.96-1.15)). However, as these HR were based on stratification by dose, their inclusion in the pooled analysis was not possible. The pooled adjusted HR for all-cause mortality calculated from the three applicable cohorts was 0.80 (95% CI 0.60-1.05), heterogeneity was statistically significant (87.6%, p<0.001) (**Figure 2**).

Risk of cardiovascular mortality

Chen et al. reported a protective effect of allopurinol on cardiovascular mortality, finding a hazard ratio in patients with gout treated with allopurinol of 0.37 (95% CI 0.01-0.48) compared to non-allopurinol users. Coburn et al. initially reported an association between increased cardiovascular-related mortality in those with escalated allopurinol dose compared to those with a stable dose for model 1 (HR 1.08, 95% CI 0.97– 1.21), but no association remained in model 2 (1.05 (95%CI 0.92-1.20)). Due to the sparsity of data related to cardiovascular mortality we were unable to conduct pooled analysis for this outcome.

Discussion

Our systematic review and meta-analysis of three studies showed no significant association between the use of allopurinol and all-cause mortality in patients with gout. The results of studies into cardiovascular mortality were contradictory and limited (preventing data pooling).

Our findings are not consistent with reports of statistically significantly decreased mortality associated with allopurinol use in hyperuricaemic patients and a protective effect against cardiovascular and chronic kidney disease in patients with gout (11-14, 20). Though not directly comparable, such findings supported our initial hypothesis that a reduction in mortality for patients with gout using allopurinol would be observed. There are, however, some important differences between the studies in our meta-analysis and those which have previously shown protective effects of allopurinol. Notably, the studies included in our

review used observational data from clinical practice, where allopurinol dosage is commonly insufficient to lower urate significantly (only 40% having treatment escalated to achieve the target serum urate level (10)). Studies which have shown a protective effect of allopurinol dosage on the risk of cardiovascular events often involve dosage of more than 600mg/day, compared to the more common 100-300mg/day found throughout normal primary care gout management. Also in the case of randomised control trials (RCT) (11), dosage of ULT was managed, observed and escalated in a more systematic way than in the cohort studies included in our review. It is possible, therefore, that the non-significant protective effect reported by our meta-analysis is related to the fact that; i) lower dosages infrequently facilitate the achievement of target serum urate levels in patients and ii) there are frequently lower levels of compliance and treatment observation in the general population compared to RCT populations.

Our findings support the existing body of evidence on the short-term safety of allopurinol (21, 22), as our included articles used large, nationally representative datasets and provided a combined sample of >10,000 patients with gout in which to examine all-cause mortality. In particular to the UK, where the majority of patients with gout are managed in primary care, Kuo et al and Dubreuil et al formed the principal weighting within the meta-analysis with data from two different primary care datasets. A key methodological difference between the studies is the use of landmark analysis by Kuo et al to address the potential for immortal time-bias, and this methodological difference may well be the cause of the disagreement between the two studies regarding risk. Though Chen et al demonstrated a protective effect of allopurinol use, their sample was small and they did not include landmark analysis. However, they attempted to avoid immortal time bias by matching for the index date of ULT prescription using a propensity score (16). It is possible that the difference in reported effects between Chen et al's study and the other three in this systematic review is due to the difference in populations.

The pooled HR of 0.80 with its confidence interval of 0.60 to 1.05 could suggest a possible small protective effect of allopurinol; however, statistical significance was not reached and the two largest of the three included studies contributed the greatest weighting in the meta-analysis and had HRs closest to 1. Further larger studies into the effect of allopurinol on both

all-cause and cause-specific mortality in patients with gout are needed. Our findings are complicated by the results of Coburn et al., who showed an increase in risk of all-cause mortality in patients with gout whose dosage was escalated, although these associations became non-significant upon closer matching of patients with dose-escalation to patients without dose-escalation.

Given the protective effects of allopurinol found in RCTs and several cohort studies, further research in this area to produce a more cohesive and conclusive view of the association between patients with gout treated with allopurinol and mortality is essential. Consideration should be given to the effect of allopurinol on mortality in specific sub-groups, such as men and women and those with different comorbidities or tophaceous gout. Also of high importance in this research would be effects of treatment adherence, as this is so low in patients with gout that it may be undermining not just the primary aims for allopurinol, but also possible secondary positive outcomes, such as a lower risk of early all-cause mortality.

We are unable to draw any conclusions on any potential role of allopurinol use in cardiovascular mortality in patients with gout. Only two articles were identified and results were varied, therefore further research is required. However, from one of these articles (19), the consideration of allopurinol dose arises as an important issue in the matter of the role of allopurinol on mortality in patients with gout. Coburn et al found no significant difference between either all-cause or cardiovascular mortality in those patients who had their dose of allopurinol escalated over two years and those whose dose remained stable. To address the fact that the majority of patients with gout using allopurinol never reach target serum urate levels, they performed a sensitivity analysis using only those patients who did reached the guideline target levels. Within this sub-sample, they found that for all-cause mortality there remained a similar HR (not reported); however, for cardiovascular mortality, though not significant, they now found a reduction in risk of 7% ((HR 0.93, 95% CI 0.76–1.14). The role of allopurinol and its dose on the risk of premature mortality (particularly cardiovascular) in patients with gout using allopurinol requires much further study.

Strengths and limitations

This is the first systematic review to examine the association between patients with gout treated with allopurinol and cardiovascular or all-cause mortality. Our search criteria were extensive (not limited by language) and included cohort studies from large, nationally representative samples using data over similar time periods to provide a more generalisable picture of the role of allopurinol on mortality in patients with gout. Risk estimates for all-cause mortality from different studies were pooled. The principal limitations of our review are the small number of articles available and statistical heterogeneity in the pooled analysis. However, despite the low number of studies, those included in this systematic review are of high methodological quality, having factored in methods for avoiding immortal time bias and confounding by indication.

Conclusion

Our systematic review and meta-analysis did not find a significant association between allopurinol use and cardiovascular or all-cause mortality. However, the small number of studies suitable for inclusion and the evidence from the wider literature that allopurinol may have cardiovascular and renal benefits, suggests that further studies into the effect of allopurinol use on mortality in people with gout are required, particularly regarding the role of allopurinol dose and the importance of reaching target serum urate levels.

Funding

References

1.	Kuo C-F, Grainge MJ, Mallen C, Zhang W, Doherty M. Rising burden of gout in the UK but continuing suboptimal management: a nationwide population study. Annals of the rheumatic diseases. 2015;74(4):661-7.

2.	Kuo C-F, Grainge MJ, Zhang W, Doherty M. Global epidemiology of gout: prevalence, incidence and risk factors. Nature reviews rheumatology. 2015;11(11):649.

3.	Chandratre P, Roddy E, Clarson L, Richardson J, Hider SL, Mallen CD. Health-related quality of life in gout: a systematic review. Rheumatology. 2013;52(11):2031-40.

4.	Clarson LE, Hider SL, Belcher J, Heneghan C, Roddy E, Mallen CD. Increased risk of vascular disease associated with gout: a retrospective, matched cohort study in the UK clinical practice research datalink. Annals of the rheumatic diseases. 2015;74(4):642-7.

5.	Kuo C-F, Luo S-F. Gout: risk of premature death in gout unchanged for years. Nature Reviews Rheumatology. 2017;13(4):200.

6.	Li-Yu J, Clayburne G, Sieck M, Beutler A, Rull M, Eisner E, et al. Treatment of chronic gout. Can we determine when urate stores are depleted enough to prevent attacks of gout? The Journal of Rheumatology. 2001;28(3):577-80.

7.	Perez-Ruiz F, Herrero-Beites AM. Evaluation and treatment of gout as a chronic disease. Advances in therapy. 2012;29(11):935-46.

8.	Hui M, Carr A, Cameron S, Davenport G, Doherty M, Forrester H, et al. The British Society for Rheumatology guideline for the management of gout. Rheumatology. 2017;56(7):e1-e20.

9.	Richette P, Doherty M, Pascual E, Barskova V, Becce F, Castaneda-Sanabria J, et al. 2016 updated EULAR evidence-based recommendations for the management of gout. Annals of the rheumatic diseases. 2017;76(1):29-42.

10.	Cottrell E, Crabtree V, Edwards JJ, Roddy E. Improvement in the management of gout is vital and overdue: an audit from a UK primary care medical practice. BMC family practice. 2013;14(1):170.

11.	Goicoechea M, de Vinuesa SG, Verdalles U, Verde E, Macias N, Santos A, et al. Allopurinol and progression of CKD and cardiovascular events: long-term follow-up of a randomized clinical trial. American Journal of Kidney Diseases. 2015;65(4):543-9.

12.   Doehner W, Schoene N, Rauchhaus M, Leyva-Leon F, Pavitt DV, Reaveley DA, et al. Effects of xanthine oxidase inhibition with allopurinol on endothelial function and peripheral blood flow in hyperuricemic patients with chronic heart failure: results from 2 placebo-controlled studies. Circulation. 2002;105(22):2619-24.

13.   Luk AJ, Levin GP, Moore EE, Zhou X-H, Kestenbaum BR, Choi HK. Allopurinol and mortality in hyperuricaemic patients. Rheumatology. 2009;48(7):804-6.

14.   Wei L, Mackenzie IS, Chen Y, Struthers AD, MacDonald TM. Impact of allopurinol use on urate concentration and cardiovascular outcome. British journal of clinical pharmacology. 2011;71(4):600-7.

15.   GA Wells BS, D O'Connell, J Peterson, V Welch, M Losos, P Tugwell. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [cited 2019] Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

16.   Chen J-H, Lan J-L, Cheng C-F, Liang W-M, Lin H-Y, Tsay GJ, et al. Effect of urate-lowering therapy on the risk of cardiovascular disease and all-cause mortality in patients with gout: a case-matched cohort study. The Journal of rheumatology. 2015;42(9):1694-701.

17.   Dubreuil M, Zhu Y, Zhang Y, Seeger JD, Lu N, Rho YH, et al. Allopurinol initiation and all-cause mortality in the general population. Annals of the rheumatic diseases. 2015;74(7):1368-72.

18.   Kuo C-F, Grainge MJ, Mallen C, Zhang W, Doherty M. Effect of allopurinol on all-cause mortality in adults with incident gout: propensity score–matched landmark analysis. Rheumatology. 2015;54(12):2145-50.

19.   Coburn BW, Michaud K, Bergman DA, Mikuls TR. Allopurinol Dose Escalation and Mortality Among Patients With Gout: A National Propensity-Matched Cohort Study. Arthritis & Rheumatology. 2018;70(8):1298-307.

20.   White WB, Saag KG, Becker MA, Borer JS, Gorelick PB, Whelton A, et al. Cardiovascular safety of febuxostat or allopurinol in patients with gout. New England Journal of Medicine. 2018;378(13):1200-10.

21.   Li S, Yang H, Guo Y, Wei F, Yang X, Li D, et al. Comparative efficacy and safety of urate-lowering therapy for the treatment of hyperuricemia: a systematic review and network meta-analysis. Scientific reports. 2016;6:33082.

22.   Ramasamy SN, Korb-Wells CS, Kannangara DR, Smith MW, Wang N, Roberts DM, et al. Allopurinol hypersensitivity: a systematic review of all published cases, 1950–2012. Drug safety. 2013;36(10):953-80.

Table 1: The characteristics, demographics and risk values of the study sample used in each included article

Author, year	Population	Study period	Sample Size	Incident gout (n)	Males (%)	Mean Age (SD)	Adjusted Hazard Ratios (95% CI)
Chen et al. (2015)	MJ Health Screening Centre Database, Taiwan	1997-2002	1,457	286	89	52.7 (15.4)	0.39 (0.22-0.70)
Coburn et al. (2016)	US Department of Veterans Affairs Health Administration (VHA)	1999-2010	111,694	6,428^	99.7	64.4 (10.5)	1.05 (0.96-1.15)*
Dubreuil et al. (2015)	The Health Improvement Network (THIN), UK	2000-2010	9,590	483	69	67	0.81 (0.70-0.92)
Kuo et al. (2015)	Clinical Practice Research Datalink (CPRD), UK	1995-2013	19,549	3519	72	64 (52-73)**	0.99 (0.87-1.12)*** 1.01 (0.92-1.09)****

^Gout patients receiving dose escalation. *This HR represents the risk of all-cause mortality in patients with gout treated with escalating doses of allopurinol compared to patients with gout on a constant dosage of allopurinol. **Median & Interquartile Range (IQR). ***1 Year Landmark analysis, ****3 Year Landmark analysis

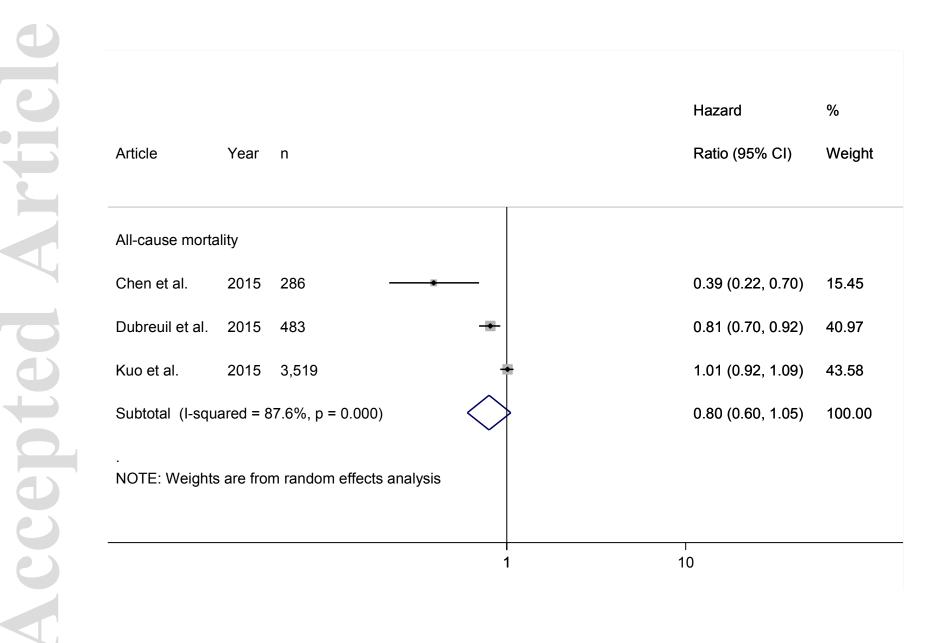**Figure 1:** Flow diagram of the number of articles at each stage of the search and screening process

Figure 2: Random Effects Meta-Analysis of hazard ratio

362
articles identified through database searches
MEDLINE: 69
EMBASE: 280
CINAHL: 13

90
duplicate articles removed

272
articles screened using title

235
articles excluded

37
articles screened using abstract

32 articles excluded:
19 non-cohort studies and reviews
6 specific populations
4 no treatment comparisons
2 no all-cause or CVD mortality outcome
1 no risk measure

5
articles screened by full text

1 article excluded:
specific population

4
articles included in systematic review

Article	Year	n	Hazard Ratio (95% CI)	% Weight
All-cause mortality				
Chen et al.	2015	286	0.39 (0.22, 0.70)	15.45
Dubreuil et al.	2015	483	0.81 (0.70, 0.92)	40.97
Kuo et al.	2015	3,519	1.01 (0.92, 1.09)	43.58
Subtotal (I-squared = 87.6%, p = 0.000)			0.80 (0.60, 1.05)	100.00

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NOTE: Weights are from random effects analysis

1   10