Cardiovascular Risk Factors and Comorbidities in Patients with Hyperuricemia and/or Gout: A Systematic Review of the Literature

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ABSTRACT. ***Objective.*** To review the available literature on the likelihood of having cardiovascular (CV) risk factors and on developing CV comorbidities in patients with gout and/or asymptomatic hyperuricemia as an evidence base for generating multinational clinical practice recommendations in the 3e (Evidence, Expertise, Exchange) Initiative in Rheumatology.

Methods. A systematic literature search was carried out using MEDLINE, EMBASE, and The Cochrane Library, and abstracts presented at the 2010/2011 meetings of the American College of Rheumatology (ACR) and the European League Against Rheumatism, searching for CV risk factors and new CV comorbidities in patients with asymptomatic hyperuricemia and/or a diagnosis of gout. Trials that fulfilled predefined inclusion criteria were systematically reviewed.

Results. A total of 66 out of 8918 identified publications were included in this review. After assessment of the risk of bias, 32 articles with a high risk of bias were excluded. Data could not be pooled because of clinical and statistical heterogeneity. In general, both for asymptomatic hyperuricemia and for gout the hazard ratios for CV comorbidities were only modestly increased (1.5 to 2.0) as were the hazard ratios for CV risk factors, ranging from 1.4 to 2.0 for hypertension and from 1.0 to 2.4 for diabetes.

Conclusion. Unlike the common opinion that patients with gout or hyperuricemia are at higher risk of developing CV disease, the actual risk to develop CV disease is either rather weak (for hyperuricemia) or poorly investigated (for gout). (J Rheumatol Suppl. 2014 Sept; 92:9–14; doi:10.3899/jrheum.140457)

Key Indexing Terms:
GOUT HYPERURICEMIA HYPERTENSION DIABETES
CARDIOVASCULAR DISEASE CANCER RENAL INSUFFICIENCY

The association of uric acid and cardiovascular disease is well known[1]. Whether an elevated uric acid is the cause or the consequence of a worse cardiovascular (CV) risk profile, however, is still unsure. To date, there is no consensus on how to deal with this association in the management of patients with gout.

This article is part of the 3e (Evidence, Expertise, Exchange) Initiative on Diagnosis and Management of Gout[2]. The objective of the current report was to systematically review the literature concerning one of the 10 selected questions as an evidence base for generating the recommendations. The question was:

> In patients with hyperuricemia and/or the diagnosis of gout, should we routinely screen for comorbidities and CV risk factors?

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MATERIALS AND METHODS

A systematic review was carried out in several steps following the guidelines for Cochrane systematic reviews[3]. First, the research question was rephrased into epidemiological terms according to the PICO (Patients, Interventions, Comparator, Outcome) method[3]. Patients were defined as adults (older than 18 years) with a diagnosis of gout or hyperuricemia. In our research question there was no intervention. The comparator was considered the healthy population without gout or hyperuricemia. The outcome variables were CV risk factors (hypertension, diabetes, dyslipidemia, and metabolic syndrome), CV disease [CVD; stroke, coronary heart disease (CHD), peripheral arterial disease (PAD)] and other comorbidities. Only comorbidities that could be screened for and treated, such as renal disease and cancer, were included in the search. As outcomes for chronic kidney disease "mortality" and "start of renal replacement therapy" were chosen. For cancer, only trials on the incidence and/or mortality of site-specific cancers were selected. We also decided to include only prospective observational studies with patients free of gout and comorbidities at baseline.

Next, a systematic literature review was conducted in MEDLINE, EMBASE, and the Cochrane Library, using a comprehensive search strategy (see Appendix 1, available from www.3egout.com). There was no time restriction; languages were restricted to those spoken by members of the 3e Initiative: English, French, Spanish, German, and Dutch. Review articles were also retrieved to identify additional references via hand search. The abstracts of the annual scientific meetings of the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) from 2010 and 2011 were also searched to find unpublished trials. Each selected study was assessed for risk of bias using a tool by Hayden, *et al*[4], designed especially for prospective cohort studies. A predefined data extraction sheet was used to extract all data from the trials.

RESULTS

A total of 8918 trials were identified with our search (Figure 1). After title and abstract screening, 117 trials were retrieved for full-text review, of which 64 met the inclusion criteria. Two congress abstracts were also included as full-text trials. Thirty-two articles with a high risk of bias were excluded. Table 1 presents a summary of the key findings of our review. More detailed tables of every outcome assessed can be found in the online Appendix, available from www.3egout.com.

Hypertension. Fifteen trials describing the risk of hypertension in patients with hyperuricemia were retrieved[5-14,15,16,17,18,19]. Six of the 15 trials had a moderate risk of bias, and the other 9 had a high risk of bias and were excluded (Table 1). Studies showed a higher risk for women than for men [hazard ratio (HR) 1.9 vs 1.4).

Diabetes. Seven trials describing the risk of diabetes in patients with hyperuricemia were retrieved[19,20,21,22,23,24,25]. Four of the 7 studies had a moderate risk of bias[19,21,22,23], and the other 3 had a high risk of bias and were excluded (Table 1). Unadjusted HR ranged from 1 to 4.8 and decreased to 1.0 to 2.4 after adjustment. The risk was higher in women.

Stroke. Fifteen trials[26-35,36,37,48,39,40] on risk of stroke in patients with hyperuricemia were retrieved. Six of the 15 studies in hyperuricemic patients had a moderate risk of bias[27,28,30,31,37,39] and the remaining 7 a high risk of bias and were excluded (Table 1). Stroke-related mortality[30,39] and stroke incidence[27,28,31,37] were investigated.

Stroke incidence and mortality were not increased. One article (moderate risk of bias) described the risk of stroke in patients with gout[41]. Mortality was not increased.

Coronary heart disease. Twenty-three trials describing the risk of manifest CHD in hyperuricemic patients[26-35,40, 42-49,50,51,53,57] were identified. Thirteen of these 23 trials had

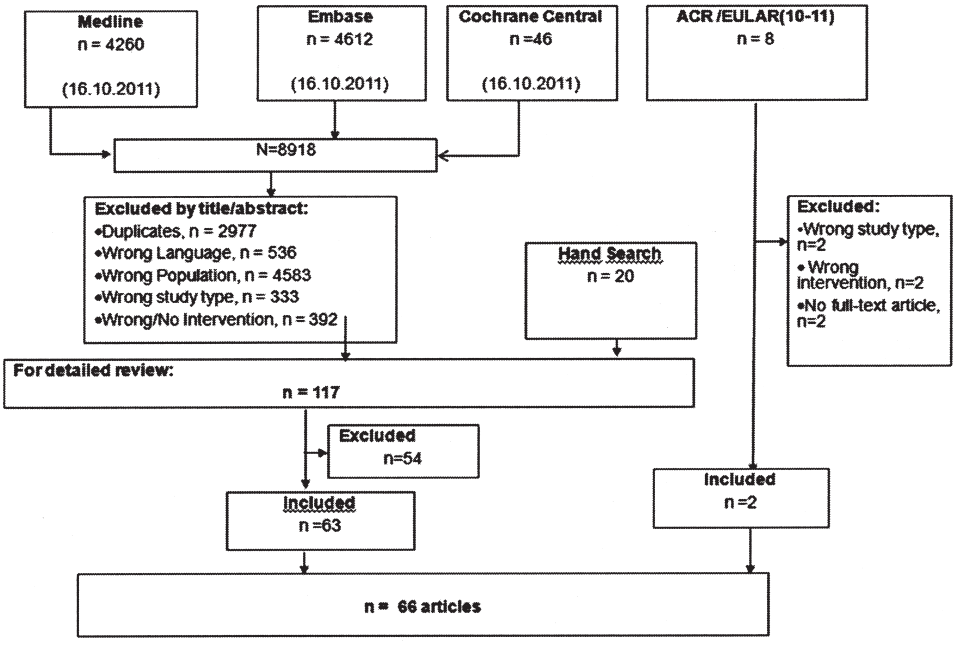

Figure 1. The systematic literature review.

Table 1. Overview of the results of the systematic literature review for each cardiovascular risk factors and each co-morbidity.

	Gender	No. Trials in Hyperuricemia/ No. Trials in Gout	HR, All Trials, range	
			Hyperuricemia	Gout
Hypertension	All	15/0	1.4–2.0	NA
	F	2/0	1.7–1.9	NA
	M	2/0	1.4–1.5	NA
Diabetes	All	7/0	1.0–2.4	NA
	F	1/0	2.0	NA
	F	2/0	1.7–1.9	NA
	M	1/0	1.07*	NA
Incidence of				
PAD	All	1/0	1.23*	NA
	F		NA	NA
	M		NA	NA
Stroke	All	6/1	1.25*–1.50*	NA
	F	1/0	1.50*	NA
	M	2/0	0.9*–1.3*	NA
CHD	All	10/4	0.7*–2.1*	1.3–1.6
	F	4/2	1.0*–2.1*	1.2*–1.4
	M	4/4	0.7*–1.5*	1.3–1.6
CKD	All	2/1	2.1–5.8	NR
	F	1/0	5.8	NA
	M	1/0	2.0*	NA
Cancer	All	2	1.0*–1.1*	1.2
	F	1/	1.0*	NA
	M	2/	1.0–1.1*	NA
Mortality due to				
Stroke	All	2/1	1.20	1.06*
	F	1/1	1.12*	1.45*
	M	1/1	1.71*	0.85*
CHD	All	13/4	1.12*–8.5*	0.97*–1.35
	F	4/2	1.3–8.5*	1.3*–1.8
	M	3/3	1.1*–1.7	1.2*–1.4*
CKD	All	0/1	NA	4.35
	F	0/1	NA	4.76
	M	0/1	NA	3.78
Cancer	All	1/0	1.4	NA
	F	0/0	NA	NA
	M	1/0	1.4	NA

*Reported HR not statistically significant. HR: hazards ratio; NA: not available; NR: HR not reported in trial — authors found not statistically significant; PAD: peripheral arterial disease; CHD: chronic heart disease; CKD: chronic kidney disease.

a moderate risk of bias[27,28,30,31,42,43,44,45,46,48,51,53]. Of those 13 trials, 6 have looked at mortality[30,45,46,49,51,53], and 7 trials investigated incidence[27,28,31,42,43,44,48]. The risk for incident CHD was not increased (Table 1). Mortality was slightly increased in women (HR 1.3) but not in men.

Nine trials described the risk of CHD in patients with gout[41,50,54,55,56,57,58,59]. Eight of these had a moderate risk of bias[41,54,55,56,57,59]. Four trials looked at CHD mortality[41,55,56,57], and another 4 examined CHD incidence[54,55,56,59]. Adjusted HR for mortality (1.4–1.8) and new CHD (1.3–1.6) were only slightly increased.

Peripheral arterial disease. One article on the risk of peripheral arterial disease in patients with hyperuricemia was found[60]. The risk was not increased (Table 1).

Cancer. Four trials describing the risk of site-specific cancer in patients with hyperuricemia were retrieved[52,61,62,63]. Three of the 4 trials had a moderate risk of bias[61,62,63] and one a high risk of bias (excluded). Mortality due to site-specific cancers[63] and incidence of site-specific cancers[61,62] were investigated. Cancer incidence was not increased. Cancer mortality was slightly increased (HR 1.4), due to cancers of the digestive tract, respiratory tract, and the nervous system (Table 1).

One article describing the risk of cancer in patients with

gout[64] revealed a moderate risk of bias. Cancer incidence (prostate) was slightly increased (HR 1.2) (see Appendix, available from www.3egout.com).

Chronic kidney disease. Three trials describing the risk of endstage kidney disease[40,65,66] in hyperuricemic patients were retrieved. Two of these 3 trials[65,66] had a moderate risk of bias. Endstage renal disease (ESRD) was defined as the start of replacement therapy (dialysis or renal transplant), and mortality was investigated in 1 trial[65]. The adjusted risk for chronic kidney disease was increased (HR 2.1–5.8), particularly in women (HR 5.8) (Table 1). Two trials describing the risk of ESRD in gout patients were retrieved[41,65]. These trials had a moderate risk of bias. Mortality was increased in 1 (HR 4.4)[41], but not in the other.

DISCUSSION

This systematic review gives an overview of the available literature on the presence of CV risk factors and other comorbidities in patients with gout and hyperuricemia, and on the risk of developing these comorbidities over time. This overview served as an evidence base for generating 1 of the 10 clinical recommendations on the diagnosis and management of gout. A detailed description of all the final recommendations can be found elsewhere[2]. Because of multiple sources of heterogeneity among the included trials, a formal metaanalysis with data pooling was not performed. This review shows that the risk to develop CV risk factors or CV diseases is not, or is only slightly, increased. With regard to cancer, the available data are too weak to support any conclusions. The risk of developing ESRD is markedly elevated in patients with hyperuricemia. With regard to gout, the results did not allow a clear conclusion. The development of ESRD in hyperuricemic patients could be explained by the deposition of urate crystals in the kidney, which contributes to the deterioration of kidney function. Two studies[67,68] monitoring kidney function in patients with gout and chronic kidney diseases who were taking urate-lowering therapies showed improvement in kidney function during treatment. Such an observation warrants further investigation on the effects of urate-lowering therapy in preventing ESRD in patients with hyperuricemia and gout.

An interesting finding in this review is that, while in men hyperuricemia does not seem to increase the risk of CV diseases, this seems to be different in women. A hypothetical explanation is that women are more sensitive to the harmful effects of uric acid on endothelial function, and to oxidative and inflammatory changes, thus affecting the risk of developing hypertension and metabolic syndrome[2].

An important limitation of the prospective studies included in this review is that patients who already had experienced a CV event were excluded from the analysis. This may lead to left-censorship bias: the event that the investigators are interested in had occurred before the start of followup. This problem can only be solved by performing large inception cohort studies, where individuals will be included as soon as hyperuricemia or gout is diagnosed. And even then, especially in the case of hyperuricemia, it will be unclear for how long the patient had already been at risk of developing the CV outcome.

During the systematic literature search, 5 metaanalyses discussing the risk of CV comorbidities in patients with hyperuricemia were identified[67,68,69,70,71]. The most important reasons for exclusion of these metaanalyses in the present study were as follows: the studies included in the metaanalyses did not always start with a "healthy cohort," of which some already had reached the endpoint, and some studies did not provide clear and useful definitions of the different uric acid categories. Another important limitation was related to the risk-of-bias assessment tool used in the metaanalysis: the Newcastle-Ottawa scale, based on which the authors of the excluded metaanalysis concluded that most included studies were of good quality. The Newcastle-Ottawa scale was designed to assess nonrandomized studies rather than prognosis studies, and thus mainly assesses the "reporting" of study methods rather than how well the study methods limit bias. However, although the risk ratio in the metaanalyses might be slightly overestimated, the main results are still in accord with our results presented here.

In summary, the well-grounded assumption that gout and hyperuricemia are risk factors for clinically manifest CV disease is based mainly on cross-sectional association studies. In the prospective cohort studies we analyzed in this review, the risk did not seem to be increased at all or was shown to be only slightly increased. Another important finding of our review is that, if an increased risk of CV disease was found in univariate analysis, this increased risk disappeared or at least was drastically lowered after adjustment for confounders. This may suggest that hyperuricemia should be seen as a risk indicator (and part of the metabolic syndrome) rather than as an individual and independent risk factor.

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