

# Assessing the risk of incident hypertension and chronic kidney disease after exposure to shockwave lithotripsy and ureteroscopy

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**In this study we sought to determine if among individuals with urolithiasis, extracorporeal shock wave lithotripsy (SWL) and ureteroscopy are associated with a higher risk of incident arterial hypertension (HTN) and/or chronic kidney disease (CKD). This was measured in a population-based retrospective study of 11,570 participants with incident urolithiasis and 127,464 without urolithiasis in The Health Improvement Network. Patients with pre-existing HTN and CKD were excluded. The study included 1319 and 919 urolithiasis patients with at least one SWL or URS procedure, respectively. Multivariable Cox regression was used to estimate the hazard ratio for incident CKD stage 3–5 and HTN in separate analyses. Over a median of 3.7 and 4.1 years, 1423 and 595 of urolithiasis participants developed HTN and CKD, respectively. Urolithiasis was associated with a significant hazard ratio each for HTN of 1.42 (95% CI: 1.35, 1.51) and for CKD of 1.82 (1.67, 1.98). SWL was associated with a significant increased risk of HTN 1.34 (1.15, 1.57), while ureteroscopy was not. When further stratified as SWL to the kidney or ureter, only SWL to the kidney was significantly and independently associated with HTN 1.40 (1.19, 1.66). Neither SWL nor ureteroscopy was associated with incident CKD. Since urolithiasis itself was associated with a hazard ratio of 1.42 for HTN, an individual who undergoes SWL to the kidney can be expected to have a significantly increased hazard ratio for HTN of 1.96 (1.67, 2.29) compared with an individual without urolithiasis.**

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**KEYWORDS:** chronic kidney disease; hypertension; shock wave lithotripsy; ureteroscopy; urolithiasis

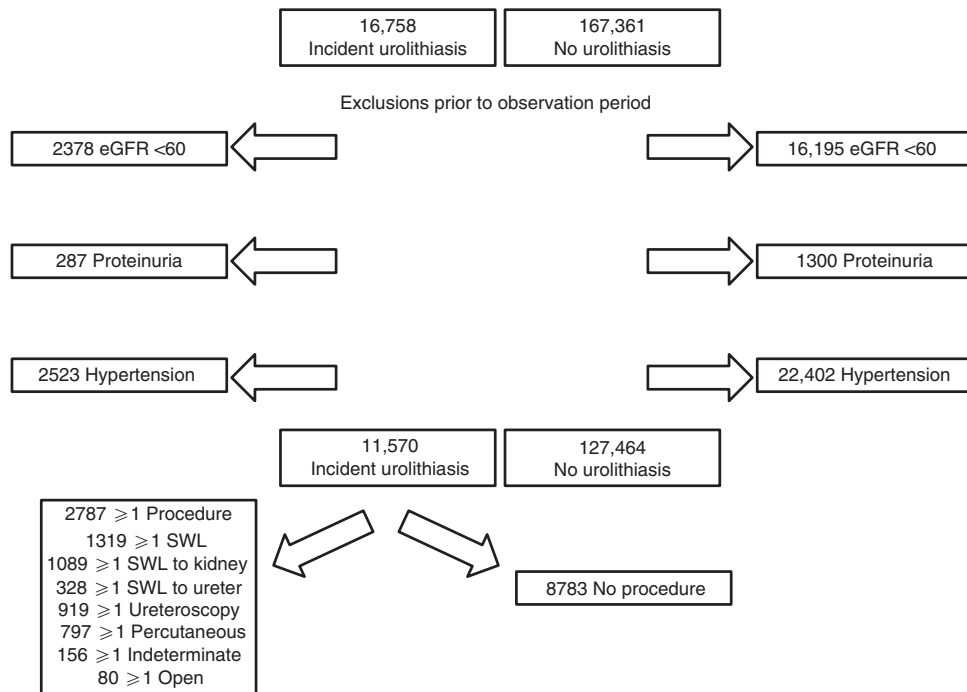
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Several studies have demonstrated that urolithiasis is associated with increased morbidity and mortality, including a higher risk of cardiovascular events,<sup>1</sup> hypertension,<sup>2,3</sup> chronic kidney disease (CKD),<sup>4</sup> and fractures.<sup>5</sup> The mechanisms by which urolithiasis might be either associated with or cause hypertension remain unclear. Altered nephron physiology predisposing to both renal calculi and hypertension, higher sodium intake among both individuals with urolithiasis and hypertension, direct renal injury from urologic interventions, and increased prevalence of metabolic syndrome, gout, or CKD in both populations have been proposed.<sup>6</sup> Similarly, the possible mechanisms that might account for the increased risk of CKD associated with urolithiasis include the following: renal parenchymal crystal deposition;<sup>7</sup> prolonged and repeated episodes of obstruction; direct damage from urologic interventions; recurrent episodes of pyelonephritis; or undiagnosed, purportedly rare inherited conditions such as cystinuria, Dent disease, or primary hyperoxaluria.

Historically, ureteric and renal calculi were managed by open surgical techniques. Currently, extracorporeal shock wave lithotripsy (SWL) and ureteroscopy (URS) account for more than 90% of these procedures.<sup>8–10</sup> Although SWL was initially thought to be harmless to the kidney,<sup>11,12</sup> subsequent animal models have demonstrated that the shock waves cause alterations in renal hemodynamics with resultant ischemic injury to the renal tubules and microvasculature.<sup>13</sup> There have also been several clinical reports of acute kidney injury,<sup>14</sup> hypertension,<sup>15,16</sup> renal morphological changes,<sup>17</sup> increased urinary inflammatory cytokines,<sup>18</sup> and transient elevation of urinary enzymes, such as N-acetyl- $\beta$ -glucosaminidase.<sup>19</sup>

To date there have not been any large epidemiological studies or randomized trials that have assessed the risk of developing CKD or hypertension after SWL or URS treatments. As a result, considerable controversy exists about whether SWL-induced acute changes ultimately result in CKD or long-term hypertension. Most studies suggest that SWL



**Figure 1 | Participant flow diagram.** eGFR, estimated glomerular filtration rate; SWL, shock wave lithotripsy.

does not result in decreased glomerular filtration rate (GFR).<sup>20,21</sup> Studies regarding SWL-associated hypertension have become a matter of debate, as there are conflicting data.<sup>15,22–25</sup> These studies were generally comprised of small cohorts of fewer than several hundred patients with short follow-up times and relied on surveys or self-reports.<sup>12,15,20,22–26</sup> Long-term outcome data on the risk of developing hypertension or CKD after URS are lacking.

The Health Improvement Network (THIN) database has been used to study hypertension,<sup>27–31</sup> CKD,<sup>32–34</sup> and urolithiasis.<sup>5</sup> The objectives of this large population-based cohort study were to determine whether, among individuals with urolithiasis, SWL is associated with a higher risk of incident hypertension and/or CKD, defined by GFR, whether the location of the SWL (kidney versus ureter) impacted these associations, and whether URS is associated with a higher risk of incident hypertension and/or CKD.

**RESULTS**

**Cohort characteristics**

Our cohort comprised 11,570 participants with incident urolithiasis and 127,464 unexposed participants, matched on age, gender, and practice, all of whom at the start of observation had not been diagnosed with hypertension or proteinuria or had a serum creatinine measure consistent with an estimated GFR <60 ml/min per 1.73 m<sup>2</sup>. A total of 2787 (24%) of the participants with urolithiasis had at least one intervention; SWL and particularly SWL to the kidney were the most common, performed in 47% and 39% of those who had an intervention, respectively (Figure 1). The baseline characteristics of the cohort are shown in Table 1. As expected

based on the established epidemiology of urolithiasis,<sup>35</sup> there were twice as many men with urolithiasis than women. Also as anticipated and as demonstrated in our prior study,<sup>5</sup> diabetes mellitus, gout, and obesity were all more prevalent among the urolithiasis population. A total of 1319 and 919 of the participants with urolithiasis had at least one SWL or URS procedure, respectively. The gender distribution and prevalence of diabetes, gout, and obesity in participants who had SWL, URS, both, or neither did not differ but age distribution did (*P*<0.001). Among the participants who had SWL, age and prevalence of diabetes, obesity, and gout in those who had SWL to the kidney, ureter, or both did not differ. The proportion of males having SWL to the ureter was greater (*P*=0.003). The median calendar year for the start of observation was 2006 (interquartile range (IQR) 2002–2009).

**Incidence of hypertension**

Over a median observation period for ascertainment of incident hypertension of 3.7 (IQR 1.6–6.8) and 3.6 (IQR 1.5–6.7) years in participants with and without urolithiasis, respectively, 1423 (12.3%) of those with urolithiasis and 10,934 (8.6%) of unexposed participants developed hypertension. Median age at the start of observation was 53 years among participants with urolithiasis who developed hypertension, and 71.8% were male, 6.9% had diabetes, and 2.8% had gout. Median age was 56 years among participants without urolithiasis who developed hypertension, and 69.0% were male, 5.3% had diabetes, and 3.3% had gout. Median time to the development of hypertension was 3.1 years (IQR 1.4–5.6), and only 43 individuals (0.03%) had

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