Pharmacologic Treatment of Kidney Stone Disease

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KEYWORDS

• Allopurinol • Citrate • Medication • Nephrolithiasis • Prevention • Thiazides • Uric acid

KEY POINTS

- Thiazide diuretics, alkali citrate, and allopurinol have been shown in randomized controlled trials to decrease recurrent calcium stone formation in patients with hypercalciuria, hypocitraturia, or hyperuricosuria, respectively.
- Thiazides and alkali citrate have been shown in randomized controlled trials to decrease recurrent stone formation in unselected stone formers.
- Urease inhibitors have been shown in randomized controlled trials to decrease struvite stone formation but side effects are common and are a major concern for these medications. Urologic surgical intervention is critical for struvite stones whenever feasible.
- There are no randomized controlled trials for uric acid stones, but alkali citrate to alkalinize urine is highly effective.
- Medical expulsive therapy has been shown in randomized controlled trials to increase spontaneous stone passage and is recommended for all ureteral stones less than 10 mm if surgical intervention is not immediately indicated.

INTRODUCTION

Nephrolithiasis is a common cause of morbidity worldwide, with lifetime prevalence reported at 5% to 10%.[1–4] In addition, recent evidence suggests that kidney stones are becoming more common.[5,6] In the absence of pharmacologic prophylaxis, recurrence rates are high, and may be in excess of 50% within 10 years of an initial stone event.[7,8] In general, prevention of stone recurrence is best directed at the underlying pathophysiology of stone formation and the appropriate regimen differs based on stone composition. Among patients with calcium stones, five major urinary risk factors increase the individual's propensity: (1) hypercalciuria, (2) hyperoxaluria, (3) hyperuricosuria, (4) hypocitraturia, and (5) low urine volume.[9,10] In addition, hypomagnesuria has also been identified as a potential contributor to calcium stone formation, although this association is less certain.[11,12] Stone prevention in patients with calcium stones is based on treatment of these urinary abnormalities. Uric acid stones are commonly treated by increasing urine pH to increase the solubility of uric acid in urine, whereas cystine stones are treated with alkalinization and thiol-binding medications to accomplish the same goal.[13–15] Finally, urease inhibitors and antibiotics may be used as prophylaxis against struvite or infection stones.[16] This

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article reviews the data on pharmacologic treatment of stone disease, with a focus on prophylaxis against stone recurrence. One of the most effective and important therapies for stone prevention, an increase in urine volume, is not reviewed because this is a dietary, not pharmacologic intervention.[17] Also review are medical expulsive therapy (MET) used to improve the spontaneous passage of ureteral stones and pharmacologic treatment of symptoms associated with ureteral stents. The goal is to review the literature with a focus on the highest level of evidence (ie, randomized controlled trials [RCT]).

CALCIUM STONES

Hypercalciuria and Thiazides

Hypercalciuria is considered an idiopathic disease, with several abnormalities of calcium balance present, including increased intestinal absorption of calcium, reduced bone mineralization, and impaired renal tubular calcium reabsorption. Primary hyperparathyroidism causes resorptive hypercalcuria. Prevention of stone recurrence in patients with idiopathic hypercalciuria is commonly accomplished with thiazide or thiazide-like diuretics, whereas resorptive hypercalcuria is best treated with parathyroid surgery.

Thiazide diuretics enhance renal calcium absorption in the proximal and distal renal tubule, and thus have been the mainstay of treatment of hypercalciuric calcium nephrolithiasis. Multiple RCTs have demonstrated the benefits of thiazide and thiazide-like diuretics in the prevention of recurrent stone disease.[12,18–22] Interestingly, only two of these trials limited their participants to those with hypercalciuria,[18,19] whereas the remainder enrolled calcium stone formers not selected based on urinary calcium excretion. All studies that followed patients for a minimum of 2 years demonstrated a benefit of thiazide treatment. These trials all examined patients with calcium oxalate stones or unspecified calcium stones. Although there are no RCTs that studied calcium phosphate stones per se, thiazides are often used for patients with calcium phosphate stones who also demonstrate hypercalciuria. A Cochrane database review that analyzed five studies (316 patients) using thiazides or thiazide-like diuretics noted a 60% decrease in the number of new stone recurrences in patients treated with thiazides compared with placebo.[23]

Potential side-effects of thiazides and thiazide-like diuretics include hypokalemia, glucose intolerance, dyslipidemia, and hyperuricemia.[24] A review of the RCTs of thiazide therapy for nephrolithiasis noted that serum glucose and lipids were evaluated in two of the studies and were unchanged by therapy, serum uric acid was increased in each of the three studies that examined it, and three of four studies that measured serum potassium noted hypokalemia. Because of this latter potential side effect, potassium supplementation should usually accompany thiazide therapy to avert hypokalemia and resultant thiazide-induced hypocitraturia.[24] Potassium is usually administered as the citrate salt but potassium chloride can also be effective. Amiloride or spironolactone are alternatives to reduce potassium loss, but the poorly soluble triamterene should be avoided.

For patients with idiopathic hypercalciuria, typical doses of these medications are as follows: hydrochlorothiazide, 50 mg daily or 25 mg twice daily; chlorthalidone, 25 to 50 mg daily; indapamide, 1.25 to 2.5 mg daily; amiloride, 5 mg daily; and amiloride/hydrochlorothiazide, 5/50 mg daily.[25] There are several common strategies to avert thiazide-induced hypokalemia, which include the addition of potassium citrate or potassium chloride (10–20 mEq orally daily to twice daily, useful in patients who also have hypocitraturia) or the use of a combination thiazide/potassium-sparing diuretic, such as amiloride/hydrochlorothiazide in patients who do not require citrate repletion. Monitoring of urine pH is also critical because elevation of the urine pH greater than 6.5 can lead to supersaturation of calcium phosphate and possible change in stone recurrence composition.

Hyperoxaluria, Magnesium, Pyridoxine, and Oxalobacter

Hyperoxaluria has often been treated with dietary rather than pharmacologic intervention. Historically, patients have been advised to restrict dietary oxalate, and some have advised a calcium-rich diet in which ingested calcium binds oxalate in the stomach and gastrointestinal tract, limiting its availability for intestinal absorption and for urinary excretion.[26] Two pharmacologic agents that may lower urinary oxalate are magnesium and pyridoxine. In both cases, however, the data are far less compelling than those that favor thiazides.

Magnesium, a cation, forms complexes with oxalate anions in the urine, reducing the oxalate available to bind calcium and form calcium oxalate calculi. Dietary magnesium may reduce intestinal oxalate absorption in a manner similar to dietary calcium, as described previously.[27] There are several noncontrolled trials in the literature evaluating magnesium oxide and magnesium hydroxide preparations that reported decreases in stone recurrence rates on these medications.[28–30] However, the single RCT that examined magnesium hydroxide versus placebo reported no difference

between treatment and placebo arms in prevention of stone recurrence.[12] Magnesium supplementation is most often used in patients with hypomagnesiuria, most of whom have bowel disease. Potential side effects of magnesium therapy include diarrhea and gastrointestinal discomfort. Although less well-studied than magnesium supplementation, calcium supplementation (calcium carbonate, calcium citrate) is another potential therapeutic target for hyperoxaluria that functions by the same mechanism, complexing with oxalate anions. Supplementation of calcium is a strategy commonly used to lower stone risk for patients with a history of Roux-en-Y gastric bypass surgery, in whom hyperoxaluria is the most common urine abnormality found on metabolic stone evaluation.[31]

The rationale for use of vitamin B_6 is that deficiencies may lead to excess urine oxalate.[32] The literature is lacking in RCTs regarding this use of pyridoxine for prevention of recurrent stone disease, but uncontrolled studies have shown that vitamin B_6 may decrease urine oxalate or stone recurrence in patients with calcium oxalate stones.[33,34] Epidemiologic studies have failed to demonstrate a benefit of vitamin B_6 supplementation in men,[35] but did show that in women, high daily doses of vitamin B_6 (>40 mg/day) may decrease risk of stone formation compared with those who ingest little or no vitamin B_6.[36] A retrospective study of pyridoxine in addition to dietary counseling in patients with hyperoxaluria noted an approximately 30% decrease in urine oxalate on follow-up 24-hour urine studies.[37]

Another potential therapy is the bacterium *Oxalobacter formigenes*, which colonizes the intestinal tract. Studies have shown that lack of colonization of this bacterium, the sole substrate of which is oxalate, may be associated with an increased incidence of calcium oxalate stone disease.[38] Early evidence demonstrated that oral *Oxalobacter* formulations could decrease urine oxalate excretion.[39] However, a recent RCT of orally administered *Oxalobacter* in patients with primary hyperoxaluria, a rare genetic calcium oxalate stone disease characterized by abnormal hepatic oxalate synthesis, failed to show differences in urine oxalate between the oral *Oxalobacter* group and placebo.[40] This potential therapy might be more successful if targeted toward patients with enteric hyperoxaluria, related to excessive absorption in the setting of inflammatory bowel disease and other causes of short bowel syndrome.

Hypocitraturia, Alkali Citrate, and Fruit Juices

Citrate is a known endogenous inhibitor of calcium oxalate stone formation; it forms soluble complexes with calcium and reduces urinary supersaturation of calcium oxalate.[41] In some cohort studies of stone formers, the incidence of hypocitraturia is in excess of 50%.[42] Several RCTs have been performed, each using a different alkali-citrate preparation.[43–45] Potassium citrate[45] and potassium-magnesium citrate[43] were both shown to significantly decrease recurrent stone formation in patients with hypocitraturia and unselected stone formers, respectively, whereas sodium-potassium citrate[44] failed to show a benefit. Potassium citrate is commercially available in tablet, liquid, and powder forms (to be mixed with water), whereas potassium-magnesium-citrate remains an investigational drug.[46] A typical starting dose of potassium citrate is 40 to 60 mEq daily in divided doses, increasing until the desired level of citraturia is reached.[46] Many clinicians monitor serum potassium 7 to 10 days after starting or changing doses of this medication. A theoretical risk of hyperkalemia exists when using potassium-based preparations, and patients with decreased glomerular filtration rate should be monitored closely when administering this medication. In addition, some patients report gastrointestinal side effects when taking potassium citrate and it is contraindicated in patients with active peptic ulcer disease. For patients with renal insufficiency or others with increased risk of hyperkalemia, sodium citrate or sodium bicarbonate may be used to increase urine citrate; however, excess sodium is another driving force in stone formation, and sodium can lead to exacerbations of congestive heart failure, hypertension, and lower extremity edema or fluid retention.

Urine citrate may also be significantly increased by ingesting beverages that are high in citrate content. In 1996, a retrospective study reported significant increases in urine citrate seen in patients who are hypocitraturic treated with a “homemade lemonade” formula (7.5 cups of water mixed with 0.5 cup of concentrated lemon juice, sweetened to taste with artificial sweetener and consumed daily).[47] Since then, several studies have tested various beverages, including other lemonade-based preparations, orange juice, pomegranate juice, lime juices, melon juice, diet sodas, and others, with equivocal results.[48,49] In addition, a single retrospective study noted that patients on lemonade therapy demonstrated a decreased stone recurrence rate.[50] Although the potential for beverage-based therapies remains of interest to patients who prefer nonpharmacologic interventions, lemonade-based therapies have been the most well-studied and some follow-up studies have produced similar results to the initial report.[48]

Hyperuricosuria and Allopurinol

Urine uric acid is thought to promote the formation of calcium oxalate stones. Uric acid reduces the solubility of calcium, called "salting out," and promotes the formation of calcium oxalate calculi.[51] Thus, hyperuricosuric calcium oxalate nephrolithiasis has traditionally been treated with allopurinol, a xanthine oxidase inhibitor that reduces endogenous uric acid production and urinary uric acid excretion. A single RCT examined stone recurrence in patients who are hyperuricosuric treated with either allopurinol or placebo and noted that the allopurinol arm demonstrated a significant decrease in stone recurrence of more than 50%.[52] This trial excluded patients with hypercalciuria and the effectiveness of xanthine oxidase inhibition in patients with hypercalciuria has not been established. Allopurinol is typically prescribed at a dose of 100 to 300 mg daily for treatment of hyperuricosuric calcium nephrolithiasis and is often used if dietary measures to reduce urine uric acid excretion (ie, dietary protein moderation) are not successful.[46] Rare side effects of this medication include Stevens-Johnson syndrome and elevated liver enzymes. For this reason, liver function tests should be monitored several months after initiation of allopurinol therapy.[53] An uncontrolled trial also demonstrated that potassium citrate is effective in decreasing stone recurrence in patients with hyperuricosuric calcium oxalate nephrolithaisis.[54]

Interesting recent research in uric acid metabolism may lead to novel therapies for hyperuricosuric nephrolithiasis and uric acid nephrolithiasis (see later) in the future. Specifically, recent reports of a new xanthine oxidase inhibitor (febuxostat) and a recombinant form of the enzyme uricase (Rasburicase) have demonstrated superiority to allopurinol in lowering serum uric acid and may also be more potent at reducing the frequency of gouty attacks.[55,56] These medications represent potential therapeutic agents for stone disease but have not been tested to date.[57]

URIC ACID STONES

At urine pH less than 5.5, uric acid has poor solubility in urine and the consequence of such acid urine may be formation of uric acid calculi. Some patients, despite having "normal" 24-hour urine uric acid levels, continue to precipitate uric acid stones if they have persistent "unduly acidic" urine. If urine pH is not increased, xanthine oxidase inhibition of uricosuria may be ineffective; at high urine pH, xanthine oxidase inhibition is redundant in addressing recurrent uric acid stones.

Urinary alkalinization is the main strategy in the treatment of uric acid calculi and is of much greater importance than reduction of uricosuria. There are no RCTs evaluating therapies for prevention of uric acid stones but alkalinization with alkali citrate is clearly so effective that randomized trials are not necessary to establish efficacy.[13,58] A common strategy for treating uric acid calculi is to alkalinize the urine as a first-line treatment and reserve the addition of allopurinol to those patients with persistently acidic urine who do not alkalinize easily, such as in the presence of bowel disease, morbid obesity, or those with hyperuricemia (eg, gout and myeloproliferative disorders). Typical starting doses include potassium citrate, 4 to 60 mEq in divided doses, or sodium bicarbonate, 1300 mg twice daily, with goal urine pH between 6.5 and 7.[46] As described previously for the treatment of hypocitraturia, sodium bicarbonate is a reasonable alternative to potassium citrate for patients with renal insufficiency or other risk for hyperkalemia. Dose titration for either medication may be done by monitoring urine pH in the physician's office or by patients at home using nitrazine paper.

STRUVITE STONES

Infection or struvite stones are those that occur as a result of chronic infection of the genitourinary tract with urease-producing bacteria, most often *Proteus*, *Pseudomonas*, *Klebsiella*, or yeast, and form at relatively high pH (typically >7). Composition of these stones is generally calcium magnesium ammonium phosphate alone, although many struvite stones also have a component of calcium phosphate (carbonate apatite or hydroxyapatite). For these stones in particular, surgical treatment is of paramount importance because it is often quite difficult to sterilize the urine and prevent recurrence if stones colonized with bacteria remain in the kidneys.

Pharmacologic prevention studies have focused on urease inhibitors and chronic suppressive antibiotics. Several RCTs have studied the urease inhibitor acetohydroxamic acid (AHA). This medication neutralizes urease, the enzyme that is central to formation of struvite stones.[16,59,60] Hydroxyurea, another potential urease inhibitor, has not been studied in a randomized trial. Each of these studies showed a significant benefit in terms of stone prevention on this agent. It should be stressed that these trials were done before the availability of the flexible ureteroscopes that today allow the endourologist access to all calyces. The role of these drugs is not well defined in an era in which stones can be more thoroughly

evacuated with ureteroscopy. AHA administration was associated with significant side effects, and the rate of severe side effects in these studies from patients on treatment ranged from 22% to 62%.[16,59,60] Known potential side effects include deep vein thrombosis, pulmonary embolism, headache, and tremulousness.[60] Chronic antibiotic suppression has been suggested in these patients, and there are retrospective data, but no randomized data, to support its use.[61] The regimen of AHA and antibiotic suppression is typically reserved for patients who are poor surgical candidates for whom the significant side effect profile of AHA may be an acceptable risk.

For patients with struvite calculi undergoing endourologic procedures, preoperative antibiotics are commonly used. Two prospective studies of antibiotics before percutaneous nephrolithotomy versus placebo in prevention of sepsis after percutaneous nephrolithotomy noted a significant reduction in patients treated with either ciprofloxacin or nitrofurantoin.[62,63] In addition, it is recommended for patients undergoing percutaneous nephrolithotomy to obtain intraoperative renal pelvis and stone culture, because these are the most accurate methods to identify causative bacteria should these patients develop fevers or sepsis postoperatively.[64]

CYSTINE STONES

Cystinuria is an autosomal-recessive condition in which those afflicted excrete cystine in large amounts in the urine. Cystine solubility is reported at 250 mg/L, but many homozygotes with the disease may excrete in excess of 1500 mg per 24 hours, leading to chronic recurrent stone formation. Mainstays of treatment are combination therapy with urinary alkalinization and thiol-binding medications. Because of the relatively high pKa of cystine (8.5), these medications may be more effective in combination than when used alone.[25]

There are no RCTs comparing any treatment with placebo for the prevention of recurrent cystine nephrolithiasis. Four noncontrolled trials have demonstrated that d-penicillamine and α-mercaptopropionylglycine (tiopronin) were effective in decreasing the number of recurrent stone events in patients who are cystinuric.[65–68] Although often well-tolerated, infrequent side effects include the following: bone marrow suppression, proteinuria with nephropathy, hepatotoxicity, aplastic anemia, drug-induced lupus, abdominal pain, diarrhea, nausea and vomiting, and anorexia. A typical starting dose of tiopronin is 200 to 300 mg three times daily (in addition to potassium citrate or sodium bicarbonate with goal urine pH 7.5), with close follow-up of 24-hour urine composition to monitor the efficacy of treatment. It is recommended to check liver function tests, complete blood counts, and urine protein/creatinine ratios at least twice a year in patients taking these drugs. A single study that compared the two medications suggested that side effects may be less frequent for tiopronin than for d-penicillamine.[25]

Captopril, a commonly used antihypertensive that contains a thiol-group, is another theoretical pharmacologic target for cystinuria. However, it does not appear in the urine in sufficient quantities to affect cysteine solubility and several small studies have yielded equivocal data on its ability to decrease urinary cystine levels.[25]

MEDICAL EXPULSIVE THERAPY

MET refers to the use of pharmacotherapy to facilitate the spontaneous passage of ureteral stones. MET is based on the principal of ureteral relaxation and the increase of hydrostatic pressure proximal to the stone.[69] Clinically, the data are most compelling for the use of α-adrenergic antagonists and calcium channel blockers. Since the original description, multiple studies have revealed the efficacy of MET in increasing stone passage rage and decreasing time to passage of stones. In 2006, a meta-analysis of RCTs reported on pooled data from nine trials (N = 693).[70] The main outcome was the proportion of patients who passed stones. The authors concluded that patients given calcium-channel blockers or α-blockers had a 65% greater likelihood of stone passage than those not given these treatments. Additionally, the addition of steroids to the various regimens led to a minor benefit. After this report, other studies demonstrated the efficacy of MET for ureteral stones.[71,72] Overall, efficacy comparing different α-blockers (tamsulosin, doxazosin, terazosin) or α-blockers with a calcium channel blocker (nifedipine) could not be determined. In another large review by Singh and colleagues,[71] MET was established as a cost-effective and well-tolerated therapy. The latter was reported in a systemic review of 16 articles on medical therapy and concluded MET was safe and efficacious for moderately sized ureteral stones. A single RCT comparing alfuzosin with placebo noted that patient discomfort was significantly decreased in the treatment arm compared with placebo.[73]

Because MET is most commonly used in the emergency department setting, Itano and colleagues[74] recently assessed the use of MET in their tertiary-care emergency department.

Of 119 patients evaluated by emergency department physicians, only 14% of patients received MET. The researchers concluded MET was underused and recommended educational interventions in the emergency department setting. The compelling evidence for the use of MET led the American Urological Association guidelines committee to recommend that patients with ureteral stones less than 10 mm in the appropriate clinical setting (without indications for surgical intervention), should be put on a MET regimen.[75] Major trials involving the use of MET are shown in **Table 1**.

PHARMACOLOGIC THERAPY FOR URETERAL STENT SYMPTOMS

Ureteral stents are commonly used to promote healing and decrease obstruction and pain after treatment of ureteral or renal stones.[76] Commonly associated side effects include lower urinary tract

Table 1
Trials of medical expulsive therapy for ureteral stones

Author/Year	Regimen	Mean Stone Size (mm)	Observation Time (d)	Mean Expulsion Time (d)	Stone Expulsion Rate (%)
1. Cha et al,[82] 2012	Tamsulosin, 0.4 mg	5.49 ± 1.31	28	7.82 ± 5.08	23/30 (76.6)
	Tamsulosin, 0.2 mg	5.73 ± 1.57		7.82 ± 5.08	23/30 (76.7)
	Alfuzosin	5.81 ± 1.26		8.22 ± 5.96	27/36 (75)
	Trospium	5.59 ± 1.44		13.56 ± 6.49	16/34 (47.1)
2. Al-Ansari et al,[83] 2010	Tamsulosin	NA	28	6.4 ± 2.77	41/50 (82)
	Placebo			9.87 ± 5.4	28/46 (61)
3. Griwan et al,[84] 2010	Tamsulosin	6.70 ± 1.60	28		27/30 (90)
	watchful waiting	6.33 ± 1.47			21/30 (70)
4. Pedro et al,[73] 2008	Alfuzosin	3.83 ± 0.95	28	5.19 ± 4.82	(73.5)
	Control	4.08 ± 0.17		8.54 ± 6.99	(77.1)
5. Vincendeau et al,[85] 2010	Tamsulosin	2.9	42		47/61 (77)
	Placebo	3.2			43/61 (70.5)
6. Ahmed and Al-Sayed,[86] 2010	Tamsulosin	4.97 ± 2.24	30	7.52 ± 7.06	25/29 (86.2)
	Alfuzosin	5.47 ± 2.13		8.26 ± 7.34	23/30 (76.6)
	Placebo	5.39 ± 1.8		13.90 ± 6.99	14/28 (50)
7. Agrawal et al,[87] 2009	Tamsulosin	6.17	28	12.3	28/34 (82.3)
	Alfuzosin	6.70		14.5	24/34 (70.5)
	Placebo	6.35		24.5	12/34 (35.2)
8. Wang et al,[88] 2008	Tamsulosin	6.5	28	6.3	26/32 (81)
	Terazosin	6.5		6.3	25/32 (78)
	Control	6.5		10.1	17/31 (55)
9. Gurbuz et al,[89] 2011	Hyoscine *N*-butyl bromide	6.13	14	10.55 ± 6.21	11%
	Alfuzosin	5.83		7.38 ± 5.55	52.9%
	Doxazosin	5.59		7.85 ± 5.11	62%
	Terazosin	5.48		7.45 ± 5.32	46%
10. Resorlu et al,[90] 2011	Doxazosin males	6.5	21		29/40 (72.5)
	Doxazosin female	7.5			28/40 (70)
11. Porpiglia et al,[91] 2000	Nifedipine + Deflazacort	5.8	28	7	38/48 (79)
	watchful waiting	5.5		20	17/48 (35)
12. Cooper et al,[92] 2000	Nifedipine	3.9	48	12.6	31/35 (89)
	Control	3.9		11.2	19/35 (54)
13. Dellabella et al,[93] 2005	Phloroglucinol		28	6.2	45/70 (64.3)
	Tamsulosin			7.2	68/70 (97.1)
	Nifedipine			6.2	54/70 (77.1)
14. Dellabella et al,[94] 2005	Tamsulosin + steroid	6.9	28	3	29/30 (96.7)
	Tamsulosin + no steroids	6.4		5	27/30 (90)

symptoms, such as urinary frequency and urgency, pain, and decreased quality of life. Multiple pharmacologic agents have been studied whose purpose is to reduce stent-related symptoms. The most common class of medications is α-blockers.[77,78] Two recent meta-analyses noted that the α-blockers tamsulosin and alfuzosin are each associated with significant decreases in stent-related lower urinary tract symptoms and pain and significant improvements in general health.[77,78] The larger of these two studies examined RCTs that included 946 patients.[78]

Two RCTs have also reported significant benefits from anticholinergic medications (extended release tolterodine[79] and solifenacin[80]). A third RCT failed to show a beneficial effect of extended release oxybutnin, although the authors noted that their sample size was small.[81]

A single study placebo-controlled study examining the use of α-blockers and anticholinergic medications alone or in combination noted that combination therapy (tamsulosin with solifenacin) was associated with the greatest reduction in stent-related symptoms.[80]

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