# **Review Article**

# Effects of intravenous sodium thiosulfate on vascular calcification in dialysis patients with end-stage renal disease: a systematic review and meta-analysis

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# Abstract

**Background:** In dialysis patients, vascular calcification is a common complication and is closely related to the morbidity and mortality of cardiovascular disease. We performed a systematic review to determine the efficacy and safety of sodium thiosulfate (STS) in the progression of vascular calcification in dialysis patients with end-stage renal disease.

**Methods:** The PubMed, Web of Science, Embase, Cochrane Library, Wanfang, CNKI, China Biology Medicine disc and Weipu databases were searched up to 9 March 2022 for clinical trials to synthesise findings on the efficacy and safety of STS in the progression of vascular calcification in dialysis patients. The primary outcome was coronary artery calcification scores (CACS) or abdominal aortic calcification scores (AACS) or Kauppila index. The secondary outcome was pulse-wave velocity (PWV). Laboratory data were shown in safety data. A random-effect model was used to provide the summary measures of effect [standardised mean difference (SMD) and 95% confidence interval (CI)].

Results: Seven randomised, controlled trials and one non-randomised, controlled trial involving 370 patients were

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Centre for Natural Products Research, Chengdu Institute of Biology, Chinese Academy of Sciences, Chengdu, China Ting Peng, MD included. Six studies reported that the progression of CACS or AACS was slower in the intravenous STS group compared with the control group (SMD -3.24, 95% CI: -5.29, -1.18, p = 0.002). Two studies showed the increase in PWV was less in the STS group compared with the control group (SMD -0.52, 95% CI: -0.92, -0.13, p = 0.009). During the trial period, a lower high-sensitivity C-reactive protein level (SMD 1.61, 95% CI: 0.19, 3.04, p = 0.03), a decrease in serum bicarbonate level (SMD 0.67, 95% CI: 0.22, 1.11, p = 0.003) and an increase in serum phosphate level (SMD-0.32, 95% CI: -0.62, -0.03, p = 0.03) were noted in the intravenous STS group compared with the control group. However, serum calcium and parathyroid hormone levels showed no difference between the two groups after the trials. The most common adverse events were temporary nausea and vomiting, which occurred in 12.5 to 75% of patients.

**Conclusions:** Intravenous STS may slow down the progression of vascular calcification and ameliorate arterial stiffness in dialysis patients. Reliably defining the efficacy and safety of intravenous STS in attenuating the progression of vascular calcification requires a high-quality trial with a large sample size.

Keywords: sodium thiosulfate, dialysis, vascular calcification

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Vascular calcification and arterial stiffness are strong risk factors for cardiovascular disease. They contribute to high morbidity and mortality rates in dialysis patients.<sup>1,2</sup> Coronary artery calcification is an agent of coronary atherosclerosis and is associated with adverse cardiovascular events.

Coronary artery calcification can be calculated by chest computerised tomography (CT) and measured by the Agatston score.<sup>3</sup> This is a confirmed method for measuring atherosclerotic plaque load and is capable of providing non-invasive quantitative information on the coronary artery vessels.

There is a dearth of treatment that can reverse or stabilise the progression of vascular calcification.<sup>4</sup> Statin therapy in dialysis patients as preventative therapy has not been shown to be beneficial.<sup>5</sup> Warfarin anticoagulation might be associated with increased calcification of atherosclerotic plaques.<sup>6</sup> Phosphate binders and bisphosphonates, which are applied for prevention and treatment of osteoporosis, have not been observed to have a constant effect on the progression of arterial calcification.<sup>7,8</sup> Studies are necessary to develop therapeutic strategies and decrease atherosclerotic disease burden.

CT measuring coronary artery calcification, plain lateral abdominal X-ray or abdominal artery calcification scores can be measured to assess vascular calcification. These parameters are strongly related to the degree of atherosclerosis, the progression of coronary heart disease and long-term mortality independent of traditional risk factors,<sup>9</sup> and the application of coronary artery calcification scores or abdominal aortic calcification scores may improve cardiovascular risk prediction in asymptomatic patients.<sup>10</sup>

Pulse-wave velocity (PWV) is the gold-standard approach for estimating arterial stiffness.<sup>11</sup> Increased PWV can be adopted to predict cardiovascular complications and mortality in dialysis patients.<sup>12</sup> To diminish the destructive effects of spiral aortic stiffness in end-stage renal disease patients, several interventions have been developed, and PWV has been used to observe the responses.

Over the years, up-to-date clinical studies targeting the cellular mechanisms of calcification have offered promising guidelines for drug development. However, vascular calcification is not expected to be reduced by any mechanism once there is deposit in the apoptic vascular cell due to inflammation and upregulation of osteogenic programme. It only can be halted or slowed down.<sup>13</sup> At present, the available treatment choices to slow down vascular calcification in dialysis patients include adequate dialytic therapy, use of non-calcium-containing phosphate binders and calcimimetic agents, active vitamin D, myoinositol hexaphosphate, denosumab, tissue non-specific alkaline phosphatase inhibitors, bisphosphonates and vitamin K.<sup>14,15</sup>

Another promising approach is the use of sodium thiosulfate (STS), a chelating agent that is commonly used to prevent cyanide poisoning.<sup>16</sup> In recent years, off-label treatment with STS has been increasingly used for the treatment of soft tissue calcifications in calcific uraemic arteriolopathy or calciphylaxis.<sup>17</sup> Studies have also found that STS might delay the development of vascular calcification in dialysis individuals.<sup>18-35</sup>

Therefore, to guide clinical practice and shed light on vascular calcification, we performed a systematic review to evaluate the safety and efficacy of intravenous STS treatment on vascular calcification, as measured by the coronary artery calcification (CACS) score or abdominal aorta calcification score (AACS), PWV, and the chronic kidney disease–mineral bone disease index.

# Methods

We performed this meta-analysis in accordance with the PRISMA guidelines.<sup>36</sup> This protocol was registered on the INPLASY website (registration number: INPLASY202230018). This systematic review was in accordance with the World Medical Association Declaration of Helsinki.

The search strategy was launched and executed by two authors (YHS and GYC) independently. We searched the

Web of Science, Embase, Cochrane Library, Wanfang, CNKI, China Biology Medicine disc and Weipu databases up to 9 March 2022, for studies to synthesise findings on the efficacy and safety of STS in the progression of vascular calcification in dialysis patients. The following search themes were used in various combinations: sodium thiosulphate, sodium thiosulfate, sodium hydrosulfite, dialysis and vascular calcification. We also scanned the reference lists of relevant included studies to identify potential eligible articles.

Based on the following inclusion criteria, two independent authors illustrated the item of studies produced by the search. Any disagreement was settled by consensus between the reviewers or proclamation with a third party (TP). The titles and abstracts of all studies were screened, and then two authors reviewed the full texts of the relevant articles.

The inclusion criteria were as follows: (1) randomised, controlled trials (RCTs) or studies that included patients presenting with vascular calcification treated with and without STS to provide a comparison between intervention and control groups; (2) studies that analysed the effect of intravenous STS on the CACS or AACS or plain lateral abdominal X-ray of adults on dialysis (age over 18 years). PWV was considered an appropriate measure of arterial stiffness. There were no restrictions regarding sample size or research duration. The exclusion criteria were case reports, review articles, letters, unpublished studies, or studies that were not conducted on clinical patients.

Quality assessment of each study was independently analysed by YHS and GYC. We used the Cochrane risk-of-bias tool to evaluate RCTs and the risk of bias in non-randomised studies of interventions to evaluate non-RCTs.<sup>37,38</sup> Two reviewers would respectively evaluate each trial with 'low', 'unclear' or 'high' risk of bias. A trial was considered at high risk of bias if one or more domains were evaluated to be high risk. A trial would be regarded as low risk of bias if all domains were judged to be low risk. Otherwise, it would be considered at unclear risk of bias. Disagreements in the scores were resolved by team discussion.

We extracted common characteristics of each study, including the first author's name, issuing time, nation, sample size, dose and duration of STS, main outcomes and adverse events. These data are provided in Table 1. We determined the mean difference and standard deviation (SD) of vascular calcification results from the STS treatment and control groups. If the mean change and SD were not provided in the study, we calculated these parameters using the median, interquartile range (IQR) and sample size.<sup>39</sup>

The primary outcome of the study was absolute changes in CACS or AACS determined using CT measuring coronary artery calcification, plain lateral abdominal X-ray, or abdominal aorta calcification. The secondary endpoint was the absolute changes in PWV levels from baseline to the end of treatment. Safety data included adverse events and changes in serum highsensitivity C-reactive protein (hsCRP), parathyroid hormone (iPTH), calcium, phosphate and bicarbonate levels monitored after treatment.

#### Statistical analysis

Statistical meta-analysis of the included studies was performed by Review Manager version 5. Due to the differences in evaluation methods and sections, we measured the standard

	Table	e 1. Main ch	naracteristic	s of the eight incl	uded studies:	STS treatment or	n vascular calcificitio	n in dialysis patients	5
Author, year	Country	Study design	Population	Intervention	Comparator	Combination therapy	Primary outcome	Secondary outcome(s)	Adverse events
Adirekkiat, <sup>29</sup> 2010	Thailand	Non-RCT	ESRD on HD with CACs ≥ 300	STS 12.5 g IV over 15–20 min after HD, 2/ week, duration 4 months ( <i>n</i> = 16)	Control group ( <i>n</i> = 16)	Phosphate bind- ers (only calcium carbonate was used) and alfacalcitriol/ calcitriol	No progression of CACs in STS group but significantly increased in control group	Total hip BMD declined in STS group	Anorexia and poor appetite in 75%, resulting in discontinuation in 10%. Sneezing in three patients (19%), two episodes of tran- sient hypotension in two patients and one episode of dizziness.
Messa, <sup>32</sup> 2014	Italy	RCT	ESRD on HD	STS 5 g IV after HD, duration 3–12 months ( <i>n</i> = 35)	Control group ( <i>n</i> = 37)	_	No effect on AC seems to be attribut- able to STS, at least when using a dose of 5 g per session	Only DM patients, treated with STS, (n = 12) displayed a significant decrease of KS (KS -8.2 ± 6.6%; $p = 0.03$ ).	-
Yu, <sup>23</sup> 2016	China	RCT	ESRD on HD with CACs > 50	STS 0.18 g/kg IV in 30 min after HD, after each HD, duration 3 months ( <i>n</i> = 15)	Control group ( <i>n</i> = 10)	Phosphate bind- ers (only calcium carbonate was used) and calcitriol	CACs increased in control group while unchanged in STS group	Significantly decreased hsCRP in STS group	No mention of side effects
Saengpanit, <sup>30</sup> 2018	Thailand	RCT	ESRD on HD with AS (CAVI ≥ 8)	STS 12.5 g IV during last hour of HD, 2/ week, duration 6 months ( <i>n</i> = 24)	Control group (n = 26)	Phosphate bind- ers (only calcium carbonate was used) and calcitriol	AS measured by CAVI signifi- cantly decreased in STS group while unchanged in control	No progression in the natural logarithm of CAC volume score in STS group, while significantly increased in control group	Anorexia and poor appetite in 12.5% of patients without discon- tinuation
Djuric, <sup>22</sup> 2019	Serbia	RCT	ESRD on HD with AACs ≥ 100	STS 25 g/1.73 m <sup>2</sup> IV during the last 15 min of HD, duration 6 months. ( $n = 26$ )	Control group (n = 29)	Phosphate bind- ers (only calcium carbonate was used) and calcitriol	Patients receiving STS exhibited a reduction of their IACS	Reduced PWV and a lower carotid intima-media thick- ness and had better preservation of echocardiographic parameters of left ventricular hyper- trophy	No adverse events possibly related to STS infusion were noted
Mao, <sup>27</sup> 2019	China	RCT	ESRD on PD with CACs ≥ 130	STS 12.8 g IV, 2/ week, duration 3 months ( <i>n</i> = 15)	Control group (n = 15)	Calcitriol was used	The CACs of control group were higher than those of before treatment and STS intervention group, there was no signifi- cant difference in CACs between STS group and before treatment	Significantly decreased hsCRP in STS group	Nausea and vomiting in 2 patients and thirst in 1 patient
Li, <sup>34</sup> 2021	China	RCT	ESRD on HD with coronary artery calcifica- tion	STS 0.18 g/kg IV in 30 min after HD, after each HD, duration 3 to 6 months ( $n = 30$ )	Control group ( <i>n</i> = 30)	Phosphate bind- ers (only calcium carbonate was used) and calcitriol	The CACs score of the observation group decreased statistically signifi- cantly compared with the control group	_	No mention of side effects
Bian, <sup>35</sup> 2021	China	RCT	ESRD on HD with coronary artery calcifica- tion	STS 0.18 g/kg IV in 30 min after HD, after each HD, duration of 6 months $(n = 25)$	Control group (n = 25)	Phosphate bind- ers (only calcium carbonate was used) and calcitriol	The CAC score of the treatment group decreased significantly after treatment	The proportion of skin pruritus, myas- thenia, bone pain, insomnia and rest- less leg syndrome in the treatment group was significantly lower than those before treatment. Significantly decreased hsCRP in STS group	No mention on side effects
STS, sodium t calcification; A sensitivity C-r MGP, matrix	hiosulfate; AS, arterial eactive pro Gla proteir	BMD, bone stiffness; C tein; IV, intr r; FGF23, f	<ul> <li>mass density AVI, cardio-a ravenous; min ibroblast grov</li> </ul>	7; CACs, coronary a inkle vascular index i, minutes; iPTH, pa vth factor 23.	rtery calcium so , ESRD, end-sta arathyroid horm	core; IACS, iliac ar age renal disease; g ione; OPG, osteopi	tery calcification score; , gram; HD, haemodial rotegerin; PINP, N-tern	PWV, pulse-wave velo ysis, PD, peritoneal dia ninal propeptide of typ	city; VC, vascular alysis; hsCRP, high- be I precollagen;

mean difference (SMD) and 95% confidence intervals (CI) for the continuous index. A *p*-value less than 0.05 represented

statistical significance.

While there were established outcomes from two or more studies, meta-analysis was applied. Statistical heterogeneity in addition to trials was investigated using the P test and p-values.

Values with p < 0.1 and P > 50% indicated significant heterogeneity. If there was a limited number of included studies or patients, the heterogeneity of the statistical test may be insensitive.

The random-effects model was adopted to analyse the pooled results. We performed sensitivity analysis using the leave-one-out method to identify the sources of heterogeneity. We generated funnel plots to detect publication bias.

## Results

We initially identified 1 892 relevant studies. A total of 184 studies were included after the initial compound search. A total of 143 studies were excluded based on the titles and abstracts. The remaining 41 studies were screened and 33 of them were excluded because they did not meet the inclusion criteria (including one duplicate study<sup>21</sup>). Ultimately, eight studies<sup>22,23,27,29,30,32,34,35</sup> involving 370 participants were included in our meta-analysis. Fig. 1 shows the search strategy.



The methodological characteristics of the eight included studies are shown in Table 1. Four studies<sup>23,27,34,35</sup> were conducted in China, two <sup>29,30</sup> were conducted in Thailand, one<sup>32</sup> in Italy and one<sup>22</sup> in Serbia. Seven of the eight studies assessed CACS or AACS via CT imaging, while one study<sup>32</sup> used plain lateral abdominal X-ray.

Six studies with 262 patients reported an increase in CACS or AACS. Compared with the control group, the results showed that STS was effective in slowing calcification of the coronary or abdominal arteries (SMD –3.24, 95% CI: –5.29 to –1.18, p = 0.002) (Fig. 2). The level of heterogeneity in the six studies was F = 98%.

Arterial stiffness was measured by PWV in two RCTs including 104 patients. Among the RCTs, the results demonstrated that the increase in PWV was slower in the STS group compared with the control group (SMD –0.52, 95% CI: –0.92 to –0.13, p = 0.009) (Fig. 3). The level of heterogeneity among the RCTs was F = 0%.

Six studies with 140 patients reported the effect of intravenous STS treatment on the serum calcium level. STS treatment did not lead to a significant change in serum calcium levels compared with the control group (SMD –0.27, 95% CI: –0.92 to 0.37, p = 0.40) (Fig. 4). The level of heterogeneity was F = 85%.

Six studies with 90 patients reported the results of intravenous STS treatment on the serum phosphate level. The results showed that there was a significant change in serum phosphate levels after STS treatment (SMD -0.32, 95% CI: -0.62 to -0.03, p = 0.03) (Fig. 5). The heterogeneity was F = 0%.

Six studies with 142 patients reported the effect of intravenous STS treatment on the serum iPTH level. The pooled results revealed that STS treatment had no effect on the serum levels of iPTH (SMD –0.47, 95% CI: –1.69 to 0.74, p = 0.44) (Fig. 6), and the level of heterogeneity was F = 95%.

Six studies with 91 patients reported the effect of intravenous STS treatment on serum levels of bicarbonate. The pooled results revealed that STS treatment led to a significant difference in the serum level of bicarbonate (SMD 0.67, 95% CI: 0.22 to 1.11, p = 0.003) (Fig. 7), and the level of heterogeneity was F = 52%.

Six studies with 114 patients reported the effect of intravenous STS treatment on serum levels of hsCRP. The meta-analysis revealed a significant difference in the serum levels of hsCRP after STS treatment (SMD 1.61, 95% CI: 0.19 to 3.04, p = 0.03) (Fig. 8), with F = 95%.

	ST	S		Con	trol			Std. Mean Difference	Std. Mean Difference	
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI	
The increase in Aga	atston scor	e								
Adirekkiat 2010	324.5	281	16	455.75	269.25	16	17.4%	-0.46 [-1.17, 0.24]		
Bian 2021	-134.82	20.25	25	51.8	4.66	25	13.8%	–12.50 [–15.11, –9.89]	· · · ·	
Djuric 2019	264	487	26	372	919	26	17.5%	-0.14 [-0.67, 0.39]	÷_	
Li 2021	-115.79	10.9	35	-66.68	1.46	35	16.8%	-6.25 [-7.41, -5.08]		
Mao 2018	-317.75	431.29	15	344.25	215.64	15	17.2%	–1.89 [–2.77, –1.01]	•	
Yu 2016	-216.75	402.12	15	-154.25	157.87	10	17.3%	-0.18 [-0.00, 0.62]		
Subtotal (95% CI)			132			130	100.0%	-3.24 [-5.29, -1.18]		
Heterofeneity: Tau <sup>2</sup> = Test for overall effect	6.20; Chl² :: Z = 3.08 (	= 172.01, p = 0.002	df = 5 (p )	0 < 0.0000	1); l² = 97%	D			-20 -10 0 10 20	
Total (95% CI)			132			130	100.0%	-3.24 [-5.29, -1.18]	Favours [STS] Favours [control]	
Heterofeneity: Tau <sup>2</sup> =	6.20; Chl <sup>2</sup>	= 172.01,	df = 5 (p	0 < 0.0000	1); l² = 97%	þ				

Fig. 2. Forest plot of the effect of the increase in CACS or AACS for STS treatment versus the control group in dialysis patients with end-stage renal disease.

	STS			Cont	rol			Std. Mean Difference	Std. Mean Difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Djuric 2019	-1.8	2.7	26	0	2.7	29	51.9%	-0.66 [-1.20, -0.11]	
Saengpanit 2018	-0.9	1.98	24	-0.02	2.54	25	48.1%	-0.38 [-0.94, -0.19]	
Total (95% CI)			50			54	100.0%	-0.52 [-0.92, -0.13]	•
Heterofeneity: Tau <sup>2</sup> = 0 Test for overall effect:	0.00; Chl² = Z = 2.62 (p	0.48, df = 0.009	= 1 (p < )	0.49); l <sup>2</sup> =	0%				+ -2 0 2 STS – Control

#### Fig. 3. Forest plot of STS treatment on the increase in PWV in dialysis patients with end-stage renal disease.

	pre-S	гs		post-S	STS			Difference	Std. Mean Difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% Cl	IV, Random, 95% Cl
Effect of intravenou	s STS on s	erum Ca	a level						
Bian 2021	2.25	0.16	25	2.19	0.21	25	17.1%	0.32 [-0.24, 0.87]	
Djuric 2019	2.37	0.2	26	2.25	0.2	26	17.2%	0.59 [0.03, 1.15]	_ <b>_</b>
Li 2021	2.28	0.22	35	2.58	0.21	35	17.4%	-1.38 [-1.90, 0.86]	
Mao 2018	2.43	0.26	15	2.51	0.19	15	15.8%	-0.34 [-0.06, 0.38]	
Saenopanit 2018	2.2	0.07	24	2.2	0.02	24	17.1%	0.00 [-0.57, 0.57]	-
Yu 2016	2.35	0.2	15	2.54	0.22	15	15.5%	-0.88 [-1.63, 0.12]	
Subtotal (95% CI)			140			140	100.0%	-0.27 [-0.92, 0.37]	
Heterofeneity: Tau <sup>2</sup> = Test for overall effect	0.54; Chl² : Z = 0.84 (	= 34.05, v = 0.40)	df = 5 (p	< 0.00001	); l² = 85%	6			
Total (95% CI)			140			140	100.0%	-0.27 [-0.92, 0.37]	-4 -2 U 2 Favours [pre-STS] Favours [post-STS]
Heterofeneity: Tau <sup>2</sup> = Test for overall effect	0.54; Chl² : Z = 0.84 (	= 34.05, v = 0.40)	df = 5 (p	< 0.00001	); l² = 85%	6			

#### Fig. 4. Forest plots of STS treatment on changes in serum calcium level in dialysis patients with end-stage renal disease.

	pre-STS			post-STS				Std. Mean Difference	Std. Mean Difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Effect of intravenous	STS on se	erum P le	evel						
Bian 2021	1.69	0.27	25	1.75	0.24	25	28.1%	-0.23 [-0.79, 0.33]	
Djuric 2019	1.41	0.4	26	1.68	0.5	26	28.1%	-0.59 [-1.14, -0.03]	
Saengpanit 2018	1.65	0.24	24	1.71	0.36	24	27.0%	-0.19 [-0.76, -0.37]	
Yu 2016	2.26	0.47	15	2.41	0.72	15	16.8%	-0.24 [-0.96, 0.48]	•
Subtotal (95% CI)			90			90	100.0%	-0.32 [-0.62, -0.03]	
Heterofeneity: Tau <sup>2</sup> = 0 Test for overall effect:	0.00; Chl² = Z = 2.14 (p	1.23, df = 0.03)	= 3 (p <	0.75); l <sup>2</sup> = (	)%				
Total (95% CI)			90			90	100.0%	-0.32 [-0.62, -0.03]	
Heterofeneity: Tau <sup>2</sup> = 0 Test for overall effect:	0.00; Chl² = Z = 2.14 (p	1.23, df = 0.03)	= 3 (p < )	0.75); l <sup>2</sup> = 0	0%				–2 –1 0 1 Favours [pre-STS] Favours [post-S

Fig. 5. Forest plots of STS treatment on changes in serum phosphate in dialysis patients with end-stage renal disease.

Adverse effects related to intravenous STS treatment among dialysis patients on vascular calcification were reported in three studies.<sup>27,29,30</sup> The most common symptoms were nausea and vomiting. Adirekkiat *et al.*<sup>29</sup> reported poor appetite or anorexia among 15 of 20 patients (75%), resulting in two patients withdrawing from the study. Two other patients complained of persistently poor appetite and anorexia lasting up to 48 hours after the injection of STS. Other side effects included sneezing (19%), two cases of transient hypotension and one case of dizziness.

Saengpanit reported anorexia and loss of appetite in 12.5% of patients, without discontinuation. Symptoms were relieved after

the dose of intravenous STS was halved in the last four months.<sup>30</sup> Other side effects included blushing in two patients and three transient events of intradialytic hypotension in two patients. No adverse events associated with intravenous STS treatment were described in other included studies.

From the eight selected studies, the SMD and 95% CIs of each outcome were assessed using the fixed-effects and randomeffects models, respectively. The discrepancy between the two outcomes was small, demonstrating that the sensitivity of the integrated results was low. We also performed sensitivity analyses by excluding one trial from the same research team as another included trial. The effect of intravenous STS treatment on the

	pre-9	STS		post-	STS			Std. Mean Difference	Std. Mean Difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% CI
Effect of intravenous	STS on s	serum iPT	H level						
Bian 2021	360.52	145.2	25	347.73	128.72	25	17.0%	0.09 [-0.46, 0.65]	
Djuric 2019	143.48	49.08	26	212.72	83.68	26	17.0%	–0.99 [–1.57, –0.42]	_ <b>_</b>
Li 2021	643.42	62.31	35	907.32	86.21	35	16.5%	-3.47 [-1.22, -2.72]	
Mao 2018	572.32	92.76	15	391.74	35.03	15	15.8%	2.51 [1.52, 3.49]	
Saengpanit 2019	151.25	79.75	26	192.75	96.25	26	17.0%	-0.46 [-1.01, 0.09]	
Yu 2016	768.5	639.63	15	1,098.5	950.02	15	16.6%	-0.40 [-1.12, 0.33]	
Subtotal (95% CI)			142			142	100.0%	-0.47 [-1.69, 0.74]	
Heterofeneity: Tau <sup>2</sup> = 2 Test for overall effect:	2.19; Chl² Z = 0.76 (	= 101.85, o p = 0.44)	df = 5 (p	< 0.00001	l); l² = 95%	D			
Total (95% CI)			142			142	100.0%	-0.47 [-1.69, 0.74]	Favours [pre-STS] Favours [post-STS]
Heterofeneity: Tau <sup>2</sup> = 2 Test for overall effect:	2.19; Chl² Z = 0.76 (	= 101.85, o p = 0.44)	df = 5 (p	< 0.00001	l); l² = 95%	D			

Fig. 6. Forest plot of STS treatment on changes in serum iPTH in dialysis patients with end-stage renal disease.



Fig. 7. Forest plot of STS treatment on changes in serum bicarbonate level in dialysis patients with end-stage renal disease.

	pre-S	TS	_	post-STS				Std. Mean Difference	Std. Mean Difference
Study or subgroup	Mean	SD	Total	Mean	SD	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl
Effect of intravenous	STS on se	erum hs(	RP						
Bian 2021	1.69	0.59	25	1.02	0.11	25	20.3%	1.55 [0.92, 2.19]	
Li 2021	7.99	0.72	35	5.03	0.43	35	19.3%	4.94 [3.97, 5.90]	
Mao 2019	7.61	3.12	15	5.44	1.97	15	20.0%	0.81 [0.06, 1.56]	+
Saengpanit 2019	2.35	1	24	2.43	1.48	24	20.5%	-0.06 [-0.63, 0.50]	
Yu 2016	7.6	3.15	15	5.17	1.27	15	19.9%	0.98 [0.22, 1.75]	
Subtotal (95% CI)			114			114	100.0%	1.61 [0.19, 3.04]	
Heterofeneity: Tau <sup>2</sup> = 2 Test for overall effect:	2.49; Chl² = Z = 2.22 (p	79.43, d = 0.03)	f = 4 (p <	< 0.00001);	l² = 95%	•			
Total (95% CI)			114			114	100.0%	1.61 [0.19, 3.04]	
Heterofeneity: Tau <sup>2</sup> = 2 Test for overall effect:	2.49; Chl² = Z = 2.22 (p	79.43, d = 0.03)	f = 4 (p <	< 0.00001);	l² = 95%	•			Favours [pre-STS] Favours [post-

Fig. 8. Forest plot of STS treatment on changes in serum bicarbonate level in dialysis patients with end-stage renal disease.

CAC or AAC score did not change, demonstrating that the pooled results were robust.

A considerable number of sources of heterogeneity existed among the studies included in this meta-analysis, mainly from different countries of origin, diverse study models, and different dosages and duration of STS administration.

We used the Cochrane risk-of-bias tool to evaluate the risk of

bias of seven RCTs, shown in Figs 9 and 10. Two studies<sup>22,35</sup> had a low risk of bias, one with some concern<sup>32</sup> and four a high risk of bias.<sup>23,27,30,34</sup> The 'high' risk of bias judgment was mainly owing to attrition bias due to blinding of participants (performance bias). Based on the risk of bias in non-randomised studies of interventions tool, the non-RCT<sup>29</sup> was evaluated as having a low risk of bias.



Fig. 9. Risk-of-bias graph: review authors' judgements about each risk-of-bias item presented as percentages across seven included RCT studies.



The funnel plots exhibited symmetric patterns for the effect of intravenous STS treatment on the CACS or AACS, as shown in Fig. 11. We conducted Egger's test to evaluate the publication bias using Stata software, which indicated no significant heterogeneity in the eight included studies.

# Discussion

Cardiovascular calcification is much more prevalent in dialysis patients than those without chronic kidney disease and it contributes to extremely high morbidity and mortality rates. Control of traditional risk factors (smoking, diabetes mellitus, hypertension and dyslipidaemia) and uraemia-related cardiovascular risk factors (hyperphosphataemia, high calcium × phosphorus



product, oxidative stress, systemic inflammation, protein energy wasting and so on) is essential to delay cardiovascular calcification in dialysis patients. However, even after the above treatment, there are still many patients who have increased calcification burden and even develop calcific uraemic arteriolopathy. Our results suggested that intravenous STS treatment might slow down the progression of vascular calcification compared to the control group in dialysis patients, with mild adverse effects.

Micro-inflammation and oxidative stress are involved in the development of vascular calcifications.40 hsCRP is an independent risk factor for CAC initiation in dialysis patients.<sup>41</sup> Several studies have proposed that STS might be beneficial in the remission of pathological calcifications or uraemic pruritus as a result of inflammatory or metabolic disorders.42-45 In addition to forming a chelate with calcium salts, intravenous STS could play a part through the production of hydrogen sulfide, nitric oxide synthase regeneration, endothelial warranty or equally by obstructing cell transformation.46-48 Interestingly, STS was demonstrated to restrain the osteoblastic trans-differentiation of adipocyte cells or human vascular smooth muscle cells prompted by hyperphosphataemia.47,48 These studies demonstrate the possibility of interplay between STS and factors influencing osteoblastic differentiation or those blocking calcification, such as Runx2, FGF-23 and matrix Gla protein.48,49

STS has also showed promising results in the treatment of other types of vascular calcification. For example, dystrophic vascular calcification can be associated with various autoimmune connective tissue diseases.<sup>50,51</sup> Systemic treatment with STS might also have had positive effects on the patient's cerebral atherosclerosis.<sup>52</sup>

Intravenous STS was reported to delay vascular calcification in dialysis patients at a dose of 25 g three times a week after dialysis, for three to six months.<sup>22</sup> However, side effects may limit the dose and frequency of STS. The tolerated dosage and diminished patient adherence to treatment may be limited by digestive symptoms (nausea, vomiting). In addition, metabolic acidosis is often related to STS use and may be critical in some situations.<sup>18,53,54</sup>

In this meta-analysis, intravenous STS resulted in a decrease in serum bicarbonate levels, which is predictable because intravenous STS is known to cause metabolic acidosis. Dose reduction to 12.5 g three times weekly has been suggested.<sup>29,30</sup> STS-induced metabolic acidosis might be solved by bicarbonate dialysate.

Finally, the negative impact on bone integrity deserves further research.<sup>55</sup> To the best of our knowledge, hypercalcaemia after treatment with intravenous STS has been described in only one study.<sup>56</sup> This aspect is worthy of further study.

The endpoints of the included studies seemed weak and lacked a comparison of death rates. Outcomes for intravenous STS in calciphylaxis are available. Treatment of uraemic calciphylaxis with systemic STS has been reported to have a significantly lower overall mortality rate than conventional treatment.<sup>56,57</sup> However, a meta-analysis analysed the pooled mortality rate resulting from seven included cohort studies on the use of intravenous STS, which was not different in patients who received STS compared with the control group.<sup>58</sup> Large-scale prospective studies are needed to validate the effect of sodium thiosulfate on long-term survival in dialysis patients.

# Limitations

This study aimed to determine the effect of intravenous STS on vascular calcification, which is very meaningful and has clinical value. Unfortunately, only eight studies were included. This metaanalysis had several limitations that should be confirmed. First, the article has limitations primarily due to the quality of the studies and the size of the data. But we believe the article in its current version has useful information for clinicians and researchers. Second, vascular calcification is a slowly progressing process, and it takes a long time to observe the effect on the progression of vascular calcification. Due to the short duration (only three to 12 months) of the eight included studies, the long-term actions of intravenous STS treatment are still unclear. Finally, there is no information on whether the decrease in these scores is sustained after STS is stopped or whether the reduction affects outcomes.

## Conclusion

This meta-analysis suggested that intravenous STS may be a promising agent to slow down vascular calcification and arterial stiffness in dialysis patients with end-stage renal disease. Given the low cost of STS and its acceptable rate of adverse effects, it should be considered when developing healthcare policies for dialysis patients. Further studies including longer follow-up times are warranted to evaluate STS effectiveness and safety and to understand the mechanisms in treating dialysis patients with vascular calcification.

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