

Intravenous sodium thiosulphate for vascular calcification of hemodialysis patients—a systematic review and meta-analysis

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GRAPHICAL ABSTRACT



What is already known about this subject?

- Vascular calcification (VC) is widely prevalent in patients with chronic kidney disease and indicative of poor cardiovascular consequences and a shorter lifetime.
- There is a dearth of treatment that can reverse or stabilize the progression of VC.

What this study adds?

- This systemic review and meta-analysis found that intravenous sodium thiosulphate (STS) may reduce the progression of VC and help ameliorate arterial stiffness in hemodialysis patients.
- Gastrointestinal symptoms (e.g. nausea) and increased anion gap acidosis were noted in the trials included, but no prolonged adverse effect was noted after the completion of STS therapy. No change in bone mineral density was found to be caused by STS.
- A lack of large and well-conducted randomized control trials (RCTs) was noted.

What impact this may have on practice or policy?

- Our findings may prompt the use of intravenous STS in treating VC among hemodialysis patients. Clinicians should be cautious in adverse effects monitoring due to the paucity of evidence in the area.
- RCTs with larger populations and higher quality should be conducted in the future.

ABSTRACT

Background. Vascular calcification (VC) is a common comorbidity among patients with chronic kidney disease (CKD), indicating major cardiovascular events. This study aimed to evaluate the effects and safety of intravenous sodium thiosulphate (STS) for VC in CKD patients.

Methods. Electronic databases were searched for clinical trials that provided data comparing outcomes among patients treated with and without STS. The PRISMA guidelines were followed. Efficacy was assessed using calcification scores and arterial stiffness. Safety was examined by analyzing adverse symptoms, electrolytes and bone mineral density (BMD). Random-effects models were performed. Meta-regression and sensitivity analysis were done. The risk of bias was assessed using the Cochrane tools.

Results. Among the 5601 publications, 6 studies involving 305 participants (mean age: 56 years, male: 56.6%) with all participants on maintenance hemodialysis met eligibility criteria. For efficacy, the progression in Agatston scores in the coronary arteries [107 patients, mean difference (MD): -241.27, 95% confidence interval (95% CI): -421.50 to -61.03] and iliac arteries (55 patients, MD: -382.00, 95% CI: -751.07 to -12.93) was lower in the STS treated group compared with controls. The increase in pulse wave velocity was lower in the STS group (104 patients, MD: -1.29 m/s, 95% CI: -2.24 to -0.34 m/s). No association was found between the change in calcification scores and STS regimen. For safety, gastrointestinal symptoms (e.g. nausea) and increased anion gap acidosis were noted. No reduction in BMD by STS was observed.

Conclusions. Intravenous STS may attenuate the progression of VC and arterial stiffness in hemodialysis patients. Large and well-designed randomized controlled trials are warranted.

Keywords: arterial stiffness, bone mineral density, chronic kidney disease, sodium thiosulphate, vascular calcification

INTRODUCTION

Vascular calcification (VC) is a strong indicator of stroke, myocardial infarction and cardiovascular (CV) mortality [1, 2]. The incidence of VC in patients with chronic kidney disease (CKD) is 2- to 5-fold that of the age-matched non-CKD population [3]. Inflammation, calcium-phosphate disturbance and uremic toxins could catalyze transformation from vascular smooth muscle cells and adventitial cells to osteoblast-like cells, which eventually results in VC [4]. VC can affect all levels of arteries, valves and heart structures but mainly indicates calcification in macrovascular circulation, primarily consisting of large- and medium-sized arteries (e.g. aorta, coronary artery and iliac artery).

In recent years, several calcification scores [e.g. Kauppila index, Agatston score, calcium volume score (CVS), etc.] have been linked to CV risks. For instance, coronary artery calcification (CAC) score is independently associated with CV consequences (heart failure, sudden cardiac death, stroke, etc.) in the general population, while abdominal aortic calcification score (AACS) has comparable values in patients treated with hemodialysis (HD) [5, 6]. However, there is a dearth of studies examining the reversal or stabilization of VC for CKD patients.

Sodium thiosulphate (STS) presents a plausible option for CKD patients with VC [7]. It was suggested as a potential treatment for calciphylaxis (featured calcification in subcutaneous arterioles and small vessels) in 2004 in a case report and was shown to prevent macrovascular calcification in uremic rats in 2008 [8, 9]. Since 2010, it has been generalized to and tested in patients with VC [10, 11]. STS has been posited to chelate calcium deposits into soluble calcium thiosulphate complexes and has vasodilatory and antioxidant activities [12]. However, severe side effects related to STS treatment have been reported anecdotally in some studies, including severe metabolic acidosis and bone mineral density (BMD)

reduction, given its potential role in inhibiting hydroxyapatite formation [13, 14].

We performed a systematic review and meta-analysis to evaluate the efficacy and safety of STS for VC in CKD patients.

MATERIALS AND METHODS

We followed the "Preferred reporting items for systematic reviews and meta-analyses (PRISMA)" guidelines and the recommendations of the Cochrane collaboration to conduct this systematic review and meta-analysis. The protocol was registered and published on PROSPERO (CRD42021235860).

Eligibility criteria

We searched for clinical trials that met the following criteria: (i) included adult patients (\geq 18 years old) diagnosed with CKD (defined as either kidney damage or a decreased glomerular filtration rate of <60 mL/min/1.73 m² for at least 3 months [15]); (ii) having VC in macrovascular circulation (e.g. coronary artery, iliac artery and aorta) as the main complication studied and the primary indication for STS treatment; and (iii) included both the patients treated with and without intravenous STS to provide a comparison between intervention and control groups. Studies were excluded if (i) they reported outcomes only from non-intravenous administration of STS (e.g. oral, intra-peritoneal, intra-lesional, etc.) or (ii) the data among CKD patients could not be extracted from the study.

Data sources and search strategy

MEDLINE/PubMed, EMBASE, Cochrane Library, Web of Science and ClinicalTrials.gov were searched using relevant terms and synonyms including "sodium thiosulphate" and "calci*" without language restriction. The controlled vocabulary terms, synonyms and the complete search strategy are listed in Supplementary data, Tables S1 and S2. We contacted the authors of eligible articles to retrieve missing data. Our data search included studies published before the end of August 2021.

Study selection and data collection process

Two authors (W.W. and I.P.-C.) screened the records independently using Endnote X20 to identify eligible studies. From the eligible studies, data were independently extracted by two authors (W.W. and I.P.-C.) regarding characteristics of studies (e.g. trial design, randomization, blinding, etc.), participants (e.g. population, age, gender, sample size, etc.), intervention and outcome measures. Discrepancies among the reviewers were rechecked by a third author (S.U.N.) and discussed to obtain a consensus.

Risk-of-bias assessment

For the studies included, risk of bias was assessed using Cochrane tools. The risk of bias in the randomized control trials (RCTs) was evaluated using "Revised Cochrane risk-ofbias tool for randomized trials (RoB 2) [16]". The risk of bias in the non-RCTs was assessed using "Risk of bias in nonrandomized studies of interventions (ROBINS-I) [17]". Two authors (W.W. and I.P.-C.) independently graded the risk of bias in the studies and consulted the third author (S.U.N.) when discrepancies arose.

Outcomes

Targeted outcomes regarding VC were collected and analyzed. For efficacy assessment, calcification scores (Agatston score, CVS and Kauppila index) and arterial stiffness measurements [pulse wave velocity (PWV) and cardio-ankle vascular index (CAVI)] were examined. For safety assessment, adverse symptoms, chronic kidney disease-mineral and bone disorder (CKD-MBD) parameters [calcium, phosphate, intact parathyroid hormone (iPTH) and 25-hydroxyvitamin D₃ (25(OH)VitD₃)], electrolytes and BMD were studied.

Data synthesis

The results were tabulated and synthesized quantitatively by performing the random-effects model. Mean difference (MD) and standard deviation (SD) of continuous variables (e.g. Agatston score, CVS, PWV, CAVI, electrolytes, etc.) were calculated and synthesized to compute a weighted MD [18]. Hedge's g as the standard mean difference was used when analyzing data from different measurements. All pooled estimates with their 95% confidence intervals (CIs) were displayed. Subgroup analyses regarding different locations of VC and BMD, as well as laboratory tests at different time points, were performed. In each subgroup analysis, difference among the group-specific overall effect size was examined using the Q_b test. A sensitivity analysis was performed to test the influence of the statistical model, effect measurements and main outcomes in our study. Meta-regression was performed to examine the impact of dose and duration of STS administration and publication year on VC measurements. Egger's test was used to measure publication bias. Heterogeneity was assessed using the I^2 test. An I^2 index >50% indicates obvious to high heterogeneity. Stata IC 16 was used for statistical analyses.

RESULTS

Description of the included studies

In total, 5601 publications were retrieved from the targeted databases among which 514 full-texts were screened. Six studies [19–24] (five RCTs and one non-randomized trial) involving 305 participants (mean age: 56 years, male: 56.6%) met our eligibility criteria. The detailed flow diagram of literature search and screening is listed in Fig. 1.

Characteristics of the six clinical trials, including population, age, gender, dialysis vintage, complicated disease, lab results and medications, are summarized in Table 1 and Supplementary data, Table S3. The six trials [19–24] were all focused on patients treated with HD. None of the patients had complicated calciphylaxis. The STS dosage ranged from 5 to 25 g, during or after dialysis, and was administrated



FIGURE 1: Flow chart of study inclusion.

2–3 times a week. Treatment duration ranged from 3 to 12 months. Medications were documented in five of the six studies. Notably, patients in the five trials only received active vitamin D and calcium-based phosphate binders for iPTH and phosphate control.

Efficacy of intravenous STS among CKD patients

Calcification scores. Comparisons of the calcification scores were categorized into subgroups according to the location of their involvement (aorta, coronary artery and iliac artery). Both the post-interventional level and the change of calcification scores from four trials [19, 21, 23, 24] were analyzed (Fig. 2). As displayed in Fig. 2B, the progression of Agatston score for coronary artery (107 patients, MD: -241.27, 95% CI: -421.50 to -61.03) and iliac artery (55 patients, MD: -382, 95% CI: -751.07 to -12.93) was lower in the STS group compared with the control group, whereas the change of Agatston score for aorta did not show a difference between the two groups (55 patients, MD: -108, 95% CI: -491.30 to 275.30). No difference between the two groups was found in each subgroup for the post-interventional Agatston

score, the post-interventional CVS and the change of CVS (shown in Fig. 2A, C and D, respectively). Meanwhile, no group difference was noticed among the overall effect sizes in subgroup analysis for all the four endpoints (P > .05) (Fig. 2A–D).

After Messa *et al.* [20], which utilized the Kauppila index to evaluate aortic calcification, was added to the meta-analysis using Hedge's g function, no difference was noted between the STS group and the control group (Supplementary data, Fig. S1). In meta-regression analyses, no correlation was found between the assessed characteristics of STS therapy and change in calcification scores (Agatston score and CVS) (P > .05) (Supplementary data, Table S4).

Arterial stiffness. Two RCTs [22, 23] studied the effect of STS on arterial stiffness. As shown in Fig. 3, the increase of PWV was lower in the STS group compared with the control group (104 patients, MD: -1.29 m/s, 95% CI: -2.24 to -0.34 m/s). No difference between the two groups was found in the post-interventional level (49 patients, MD: -0.51, 95% CI: -1.03 to 0.01) or the change (49 patients, MD: -0.46, 95% CI: -0.98 to 0.06) of CAVI.

Table 1. Chara	acteristics of the a	six clinical tria	ls for VC								
Study ID	Study design	Country	Population	No. of par- ticipants (T:C)	Age (T versus C) (mean ± SD, years)	Gender (T versus C)	Dialysis vintage (T versus C)	STS treatment	Control treatment	Duration	Outcome measurements
Adirekkiat et al. [19]	Non- randomized trial	Thailand	HD patients (CAC score ≥300)	16:16	59.6 ± 14.4 versus 60.4 ± 11.5	11M, 5F versus 8M, 8F	44.7 ± 33.7 ^a mo versus 47 2 + 28 5 ^a mo	12.5 g i.v. twice a week over 15-20 min after HD treatment was	Usual care	4 mo	Agatston score
Messa et al. [20]	RCT	Italy	HD patients	43:43	NA	NA	NA NA	5 g i.v. at the end of each dialvsis session	Usual care	12 mo	Kauppila index
Yu <i>et al.</i> [21]	RCT	China	HD patients (CAC score ≥50)	17:10	ΝΑ	NA	7 (4–23) ^b years in the whole population	0.18 g/kg dissolved in 100 mL saline i.v. 3 times a week for 30 min after every HD session	Usual care	3 mo	Agatston score
Saengpanit et al. [22]	RCT	Thailand	ESRD on HD with CAVI ≥8	24:26	50.4 ± 9.5 versus 54.4 ± 10.7	12M, 12F versus 16M, 10F	69 (38–110) ^c mo versus 55 (30–101) ^c mo	12.5 g during the last hour of HD twice a week	Usual care	6 mo	CVS; PWV; CAVI
Djuric et al. [23]	RCT	Serbia	ESRD on HD with AACS ≥100	30:30	63.8 ± 13.2 versus 64.1 ± 9.7	17M, 13F versus 21M, 9F	104.4 \pm 80.5 ^a mo versus 103.7 \pm 75.1 ^a mo	25 g/1.73 m ² dissolved in 100 mL saline i.v. during the last 15 min of every HD session	100 ml of 0.9% saline	6 mo	Agatston score; CVS; PWV
Bian <i>et al.</i> [24]	RCT	China	HD patients without severe infection, diabetes, hy- percalcaemia, or iPTH <150 pg/mL	25:25	52.1 ± 20.8 versus 52.5 ± 19.4	12M, 13F versus 12M, 13F	29 (4– 101) ^d mo versus 30 (3–107) ^d mo	0.18 g/kg dissolved in 100 mL normal saline three times a week	Usual care	6 mo	Agatston score; CVS; PWV
ID: identity; T: tr	reatment group; C: c	control group; ESI	RD: end-stage renal di	sease; M: male; F: f	ſemale; i.v.: intravenou	s; mo: months; and N/	A: not available.				

^aMean±SD. ^bMedian (range). ^cMedian (IQR1-IQR3). ^dMedian (P2.5-P97.5).

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FIGURE 2: Meta-analysis of the effect of STS on Agatston score and CVS in patients with VC. Calcification scores in different locations were synthesized. No difference was found in both post-interventional Agatston score and CVS (**A** and **C**). The increase in Agatston score was lower in the STS group compared with the control group for coronary artery (107 patients, MD: -241.27, 95% CI: -421.50 to -61.03) and iliac artery (55 patients, MD: -382, 95% CI: -751.07 to -12.93) (**B**). The change in CVS was not different between the two groups (**D**).

Safety of intravenous STS among CKD patients

Adverse symptoms. In the four studies [19, 21–23], which reported adverse symptoms related to STS treatment, gastrointestinal (GI) symptoms (e.g. anorexia, poor appetite, nausea and vomiting) were the most commonly observed (25.9%), followed by hypotension (4.7%), sneezing (4.7%), flushing (2.3%), dizziness (2.3%) and excessive thirst (1.2%) (Table 2). The study [19] with the highest frequency of GI symptoms (75%) employed post-dialysis administration and short infusion times (15–20 min).

CKD-MBD parameters. As shown in Fig. 4, four RCTs [21-24] measured calcium, phosphate and iPTH levels, while two of them [21, 22] documented $25(OH)VitD_3$ levels as well. The laboratory values were measured before dialysis at baseline, while on STS treatment (during the trials) and at the completion of the trials (after the trials). The point values (during or after the trials) and the changes from the baseline were compared between the STS group and the control group, respectively. During the trials, calcium, phosphate and iPTH were comparable between the STS group and the control group,

and there were no significant changes in these parameters. The mean level of $25(OH)VitD_3$ in the STS group is less than that of the controls (49 participants, MD: -5.80 ng/mL, 95% CI: -9.59 to -2.01 ng/mL) during the trials, but no difference was noticed in the changes from baseline between the two groups (49 participants, MD: -0.40 ng/mL, 95% CI: -4.19 to 3.39 ng/mL). After the trials, the post-interventional levels and the change of serum calcium, serum phosphate, blood iPTH and blood $25(OH)VitD_3$ in the STS group showed no difference between the two groups.

Electrolytes. In Adirekkiat *et al.* [19], serum sodium, chloride, bicarbonate and anion gap were found to be changed immediately after the infusion of STS. When comparing the electrolyte levels during the entire STS therapy with baseline levels, Adirekkiat *et al.* [19] found an elevation in pre-dialysis serum anion gap and sodium in 16 patients treated with HD undergoing a 4-month STS therapy. Serum electrolytes in the control group were also reported in three trials [21–23] during or after the trials. As displayed in Fig. 5, no significant difference was found between the STS group and the control



FIGURE 3: Meta-analysis of the effect of STS on PWV and CAVI in patients with VC. No difference was found in the post-interventional PWV between the two groups (**A**). The increase in PWV was lower in the STS group compared with the control group (104 patients, MD: -1.29 m/s, 95% CI: -2.24 to -0.34 m/s) (**B**). No difference in the post-interventional level or the change of CAVI was found between the two groups (P > .05) (**C** and **D**).

Table 2. Adverse symptoms related to STS treatment among included studies

Study ID	No. of participants	GI symptoms	Hypotension	Sneezing	Flushing	Dizziness	Thirsty
Adirekkiat et al. [19]	20	15 (anorexia and poor appetite)	2	3		1	
Yu et al. [21]	15	3 (nausea and vomiting)		1		1	1
Saengpanit et al. [22]	24	3 (anorexia and poor appetite)	2		2		
Djuric et al. [23]	26	1 (nausea)					
Total	85 (100%)	22 (25.9%)	4 (4.7%)	4 (4.7%)	2 (2.3%)	2 (2.3%)	1 (1.2%)

ID: identity; No.: number.

group in serum sodium, potassium, chloride and bicarbonate during or after the trials. During the trial period, a higher anion gap (49 participants, MD: 3.00 mmol/L, 95% CI: 1.03 to 4.97 mmol/L) and a larger increase in the anion gap (49 participants, MD: 2.50 mmol/L, 95% CI: 0.53 to 4.47 mmol/L) were noted in the STS group compared with the control group. However, anion gaps showed no difference between the two groups after the trials.

BMD. Two studies [19, 21] reported BMD in the STS and control groups. Yu *et al.* [21] showed that no significant change was observed in both groups, but the data were not retrievable. Adirekkiat *et al.* [19] reported a decline in the total hip BMD in the treatment group, but no comparison between the two groups was conducted. The lumbar and the total hip BMD in Adirekkiat *et al.* [19] were extracted and compared between the STS group and the control group. As presented in Fig. 6, the post-trial levels and the changes were not significantly different between the STS group and the control group for both the lumbar and total hip BMD values. In addition, no significant difference was found in the effect size between the two locations (lumbar and total hip).

Sensitivity analysis

Analyses were repeated using a fixed-effect model in which little differences were noted in the overall effect sizes. Furthermore, we performed sensitivity analyses on the impact of single studies. The overall effect size and its 95% CIs when omitting the denoted study are presented in Supplementary data, Fig. S2. For the change in Agatston score using Hedge's *g*, omitting Messa *et al.* [20] resulted in lower progression in the STS group. No change in the conclusion or direction of other results was noticed.

Heterogeneity

Various sources of heterogeneity were noted among the studies included in this analysis, mainly from different countries of origin, diverse study designs, various dosages, timing and duration of STS administration and distinct outcome measures. Based on the I^2 test, obvious or high heterogeneity was observed in data related to blood 25(OH)VitD₃, serum calcium, serum bicarbonate and serum anion gap.

Risk-of-bias assessment

Risk-of-bias assessment for the five RCTs [20-24] using the RoB 2 tool is shown in Fig. 7. The study by Bian *et al.* [24] had a low risk of bias, while the others were with some concern [20] or high risk of bias [21-23]. Based on the ROBINS-I tool, the non-RCT [19] was evaluated as having a low risk of bias (Fig. 8).

Egger's tests were performed to evaluate publication bias. As presented in Supplementary data, Table S5, no small study effect was discovered in our study.

Δ	Post-interv	entional Serum Calcium (m	mol/l)		R Change in S	erum Calcium (mmol/I)		
Study	Treatment C N Mean SD N	Control Mean SD	Mean Diff. with 95% CI	Weight (%)	Treatment Control	20	Mean Diff.	Weight
After trial	22)	8.53			After trial	50	with 95% CI	(%)
Saengpanit, D. 2018	24 2.2 .02 25	2.2 .02	0.00 [-0.01, 0.01]	84.29	Saengpanit, D. 2018 24 .16 .39 25 .03 .	42 -	0.13 [-0.10, 0.3	6] 15.63
Yu, Y. 2016 (21)	15 2.54 .22 10	2.41 .22	-0.03 [-0.14, 0.08]	0.95	Djuric, P. 2020 26 .26 .48 29 .01 . Yu Y 2016 15 16 71 10 -03	29 — — — — — — — — — — — — — — — — — — —	0.25 0.04, 0.4	6] 16.59
Bian, Z. 2021 ⁽²⁴⁾	25 2.19 .21 25	2.18 .21	0.01 [-0.11, 0.13]	0.78	Bian, Z. 2021 ⁽²⁴⁾ 25 .06 .23 25 .06	29 -	0.00 [-0.15, 0.1	5] 21.74
Heterogeneity: $\tau^2 = 0$. Test of $\theta = \theta$: $O(2) =$	00, l ² = 0.03%, H ² = 1.00	D 🔶	0.00 [-0.01, 0.01]		Heterogeneity: $\tau^2 = 0.01$, $l^2 = 35.03\%$, $H^2 = 1.54$	•	0.11 [-0.02, 0.2	5]
test of $\theta_i = \theta_j$. $G(3) =$	2.43, p = 0.49				lest of $\theta_i = \theta_j$: Q(3) = 3.95, p = 0.27			
During trial	22) 24 2.2 07 25	22 02	[E0.0. E0.0-1.00.0	12 57	During trial	26 -	-0.161-0.21 -0.0	1 21 60
Bian, Z. 2021 (24)	25 2.23 .18 25	2.22 .18	0.01 [-0.09, 0.11]	1.07	Bian, Z. 2021 25 .06 .26 25 .1 .	42 -	-0.04 [-0.23, 0.1	[] 21.09 [] 17.94
Heterogeneity: $\tau^2 = 0$.	.00, l ² = 0.00%, H ² = 1.00	0 🔶	0.00 [-0.03, 0.03]		Heterogeneity: $\tau^2 = 0.00$, $I^2 = 0.00\%$, $H^2 = 1.00$	+	-0.12 [-0.23, -0.0	0]
Test of $\theta_i = \theta_i$: Q(1) =	0.04, p = 0.85				lest of $\theta_i = \theta_j$: $Q(1) = 0.94$, $p = 0.33$			
Overall		•	0.00 [-0.01, 0.01]		Overall	•	0.03 [-0.10, 0.1	5]
Heterogeneity: $\tau^2 = 0$. Test of $\theta = \theta$: $Q(5) =$.00, l ² = 0.04%, H ² = 1.00 2.47, p = 0.78	D			Heterogeneity: $\tau^2 = 0.01$, $t^2 = 59.85\%$, $H^2 = 2.49$ Test of $\theta_i = \theta_i$: Q(5) = 12.04, p = 0.03			
Test of group differen	ces: Q ₂ (1) = 0.00, p = 0.9	97			Test of group differences: $Q_{b}(1) = 6.26$, p = 0.01		_	
		1 0 .1 .2	.3			5 0 .5	1	
Random-effects REML Sorted by: _meta_id	model				Sorted by: _meta_id			
С	Post-interve	ntional Serum Phosphate (r	nmol/l)		D Change in Se	rum Phosphate (mmol/l))	
	Treatment C	Control	Mean Diff.	Weight	Treatment Control	-	Mean Diff.	Weight
After trial	N Mean SD N M	Mean SD	with 95% CI	(%)	Study N Mean SD N Mean S After trial	SD	with 95% CI	(%)
Saengpanit, D. 2018	24 1.84 .39 25	1.87 .42	-0.03 [-0.26, 0.20]	11.72	Saengpanit, D. 2018 24 .16 .39 25 .03	42 —	0.13[-0.10, 0.3	6] 15.63
Djuric, P. 2020 (23)	26 1.68 .5 29	1.45 .3	0.23 [0.01, 0.45]	12.34	Djuric, P. 2020 ⁽²³⁾ 26 .26 .48 29 .01 .	29	0.25 0.04, 0.4	6] 16.59
Bian, Z. 2021 (24)	25 1.75 .24 25	1.76 .29	-0.01 [-0.16, 0.14]	27.69	Bian, Z. 2021 ⁽²⁴⁾ 25 .06 .23 25 .06 .3	29 -	0.00 [-0.15, 0.1	5] 21.74
Heterogeneity: $\tau^2 = 0$.	01, l ² = 29.27%, H ² = 1.4	H 🔶	0.06 [-0.08, 0.19]		Heterogeneity: $\tau^2 = 0.01$, $l^2 = 35.03\%$, $H^2 = 1.54$	•	0.11 [-0.02, 0.2	5]
Test of $\theta_i = \theta_j$: Q(3) =	3.74, p = 0.29				Test of $\theta_i = \theta_j$: Q(3) = 3.95, p = 0.27			
During trial	(2)	-			During trial			
Saengpanit, D. 2018 Bian, Z. 2021 ⁽²⁴⁾	24 1.78 .26 25 25 1.75 .25 25	1.78 .26 -	0.00 [-0.15, 0.15]	28.43	Saengpanit, D. 2018 2406 .26 25 .1 . Bian, Z. 2021 25 .06 .26 25 .1 .	26 – – – 42 – – –	-0.16 [-0.31, -0.0	1] 21.69 5] 17.94
Heterogeneity: $\tau^2 = 0$.	00, l ² = 0.00%, H ² = 1.00	-	-0.01 [-0.13, 0.10]		Heterogeneity: $\tau^2 = 0.00$, $l^2 = 0.00\%$, $H^2 = 1.00$	+	-0.12 [-0.23, -0.0	0]
Test of $\theta_i = \theta_j$: Q(1) =	0.06, p = 0.80				Test of $\theta_i = \theta_j$: Q(1) = 0.94, p = 0.33			
Overall		•	0.02 [-0.06, 0.10]		Overall	*	0.03 [-0.10, 0.1	6]
Heterogeneity: $\tau^2 = 0$. Test of $\theta = \theta : O(E) =$	00, l ² = 0.00%, H ² = 1.00				Heterogeneity: $\tau^2 = 0.01$, $l^2 = 59.85\%$, $H^2 = 2.49$ Test of $\theta = \theta$: $O(5) = 12.04$, $p = 0.03$			
Test of aroup different	ces: Q.(1) = 0.57. p = 0.4	15			Test of group differences: $Q_{1}(1) = 6.26$, $p = 0.01$			
		5 0	.5				7	
						5 0 .5		
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Random-effects REML Sorted by: _meta_id EF Study After trial Saengpanit, D. 2018 ⁽²²⁾ 2 Djuric, P. 2020 ⁽²³⁾ 2	model Post-interventional Treatment C N Mean SD N M 24 208.7 302.2 25 26 220.6 262.7 29 13	l intact parathyroid hormon control ean SD 237 208.8 332 162.6	e (pg/ml) Mean Diff. with 95% Cl -28.30 [-174.30, 117.70] 87.40 [-29.64, 204.44]	Weight (%) 8.01 12.46	Bandom-effects REML model Change in intact par Treatment Note: N N Nem: S0 N Mem: S1 Nutber trial N Mem: S2 N Mem: S1 Samper trial 0.2016 ²² / ₂₄ 47 302.2 25 103 200 Operating trial 0.27 26.27 27.1 26.27 27.1 26.27 21.9 10.2 26.27 26.27 26.27 26.27 26.27 26.27 26.27 26.3 26.27 26.27 26.3 26.27 26.27 26.3 26.27 26.27 26.37 26.27 26.37 2	rathyroid hormone (pg/r	mi) Mean Diff. with 95% Cl 36.70 [-109.30, 182 53.10 [-63.94, 170	Weight (%) 70] 8.01 14] 12.46
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$\label{eq:response} \begin{array}{c} \text{Random-effects REML}\\ \text{Sorted by:meta_id} \\ \hline \\ \textbf{E} & \textbf{F} \\ \text{Study} \\ \text{After trial} \\ \text{Saengpanit, D. 2018^{(2)}} \\ \text{Suby, P. 2020^{(23)} } \\ \text{Qluric, P. 2020^{(23)} } \\ \text{Heterogeneity: } \textbf{t}^{=} 0.00 \\ \text{Test of } \theta_i = \theta_j^- \textbf{Q}(3) = 1.8 \end{array}$	model Post-interventional Treatment N Mean SD N M 4 208.7 302.2 25 46 2206 262.7 29 11 5 1093.5 948.9 10 11 15 347.7 128.7 25 34 , P = 0.00%, H ^a = 1.00 9, p = 0.60	lintact parathyroid hormon como 207 208.8 227 208.8 228 208.2 228 208.2 324 128.7 \$	e (pg/ml) Mean Diff, with 95% CI -28.30 [+174.30, 117.70] -751.85, 713.85] 4.30 [-66.49, 75.09] 18.29 [-37.50, 74.07]	Weight (%) 8.01 12.46 0.32 34.05	Bandom-effects REML model Change in intact par Treatment Study N Mem SD N Mem SI Study N Mem SD N Mem SI Control Study N Mem SI N Mem SI Control Study N Mem SI N Mem SI Control Study N Mem SI African SI SI Mem SI SI Mem SI SI Mem SI	-5 0 .5 athyroid hormone (pg/s D 18 -■- 1 12 - 1 12 - 1 57 ■ 1	Mean Diff. with 95% Cl 36.70 [-109.30, 162 53.10 [-63.94, 170 19.70 [-613.15, 652 -2.00 [-7.2.79, 66 16.87 [-38.91, 72	Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66]
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Random-effects FIEM. Sotted by:meta_id Study After trial Saenganit. 0.2018 ²⁰²¹ ; Junic, P. 2020 ¹⁰²¹ ; Yu, Y. 2018 ¹⁰¹ ; Bian, Z. 2021 ¹⁰¹ ; Saenganit. 0.2018 ¹⁰²¹ ; Bian, Z. 2021 ¹⁰¹ ; Saenganit. 0.2018 ¹⁰²¹ ; Bian, Z. 2021 ¹⁰¹ ; Bian, Z. 2021 ¹⁰¹ ; Bian, Z. 2021 ¹⁰¹ ;	Model Cost-interventional Treatment Noman 20 10 </td <td>Lintact parathyroid hormon Control 227 208.8</td> <td>e (pg/ml) Mean Diff. with 95% C1 -28.30 [-174.30, 117.70] 87.40 [-28.64, 204.44] -19.00 [-751.85, 713.85] 4.30 [-68.49, 75.09] 18.29 [-37.50, 74.07] -36.30 [-163.87, 91.27] 9.30 [-60.85, 79.45]</td> <td>Weight (%) 8.01 12.46 0.32 34.05 10.49 34.68</td> <td>Bandom-effects REML model Change in intact par Treatment Provide Stream St</td> <td>-3 0 3 athyroid hormone (pg/ b b b c c c c c c c c c c c c c c c c</td> <td>mi) Mean Diff. with 95% C1 36.70 [-109.30, 182 53.10 [-63.94, 170 19.70 [-61.315, 825 23.00 [-27.28, 68 16.87 [-38.91, 72 28.70 [-98.87, 156 2.90 [-67.25, 73</td> <td>Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68</td>	Lintact parathyroid hormon Control 227 208.8	e (pg/ml) Mean Diff. with 95% C1 -28.30 [-174.30, 117.70] 87.40 [-28.64, 204.44] -19.00 [-751.85, 713.85] 4.30 [-68.49, 75.09] 18.29 [-37.50, 74.07] -36.30 [-163.87, 91.27] 9.30 [-60.85, 79.45]	Weight (%) 8.01 12.46 0.32 34.05 10.49 34.68	Bandom-effects REML model Change in intact par Treatment Provide Stream St	-3 0 3 athyroid hormone (pg/ b b b c c c c c c c c c c c c c c c c	mi) Mean Diff. with 95% C1 36.70 [-109.30, 182 53.10 [-63.94, 170 19.70 [-61.315, 825 23.00 [-27.28, 68 16.87 [-38.91, 72 28.70 [-98.87, 156 2.90 [-67.25, 73	Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68
Randform-Rifed's FRML Soutod by:meta_i_d Study After trial Seergrant, D. 2018 ²² ; Dpire, P. 2020 ²¹ Hebrogeneity: T ⁱ = 0.00 Test of a = 0; c)(a) = 1.5 During trial Sam, Z. 2021 ⁶⁰ Hebrogeneity: T ⁱ = 0.00 Stanz, Z. 2021 ⁶⁰ Hebrogeneity: T ⁱ = 0.00	model Post-interventional Teatment Commonstant Value V	Lintact parathyroid hormon Centrol 227 208.8	e (pg/ml) Mean Diff. with 85% Cl -28.30 [-174.30, 117.70] 87.80 [-2844, 204.44] -1800 [-751.85, 771.84] -36.30 [-168.87, 79.127] -36.30 [-168.87, 91.27] -39.30 [-06.85, 78.45] -1.29 [-62.76, 00.19]	Weight (%) 8.01 12.46 0.32 34.05 10.49 34.68	Mandom-effects REML model Change in intact part Treatment Treatment State N Market part Normalization State State Treatment Treatment State State State State State State State <td>-3 U .3 athyroid hormone (pg/s D 1.8 -■- 1.2 </td> <td>Mean Diff. with 95% Cl 36.70 [-109.30, 142 53.10 [-63.94, 170 19.70 [-61.315, 852 -2.00 [-72.79, 68 16.87 [-38.91, 72 28.70 [-98.87, 156 2.90 [-67.25, 73 8.89 [-52.58, 70</td> <td>Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68 36]</td>	-3 U .3 athyroid hormone (pg/s D 1.8 -■- 1.2 	Mean Diff. with 95% Cl 36.70 [-109.30, 142 53.10 [-63.94, 170 19.70 [-61.315, 852 -2.00 [-72.79, 68 16.87 [-38.91, 72 28.70 [-98.87, 156 2.90 [-67.25, 73 8.89 [-52.58, 70	Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68 36]
Randform-effects FEML Societa by:meta_jet Study	model Testimet C V0.51-interventional N Mean 50 N Main 50.02 25 100.05 90.22 25 100.05 90.22 25 100.05 90.22 25 100.05 90.22 25 100.05 91.7 128.7 25 100.05 91.7 128.7 25 4 161.3 214.3 25 1 5 364.7 128.2 25 3 16.35 214.3 25 1 16.3 24.4 25 3	Lintact parathyroid hormon Control 227 208.8	e (pg/ml) Mean Dif. with 95% Cl -08.30 [17.30, 0 117.70] 07.80 [-25.64, 204.44] -19.00 [-751.85, 713.68] -3.83 [-468.47, 75.09] -3.63.30 [-163.87, 91.27] -3.63.30 [-163.87, 91.27] -1.29 [-62.76, 60.19]	Weight (%) 8.01 12.46 0.32 34.05 10.49 34.68	Bandom-effects REML model Stady Change in Intact part Treatment N Make So intact part Treatment Nator full Notice Colspan="2">Colspan="2" Seergeant D, 2016 ²⁷ 24 7 302.2 25 10.3 300 Joiner, P. 2020 ²⁷ 3 67 25 24.8 10 26.5 893 Manz, 2202 ¹⁽²⁾ 15 32.5 94.9 10 26.5 893 Hoterogenelity: "= 0.00, "= 0.00%, H = 1.00 126 146.7 25 -5.8 128 49.7 25 -4.8 25 -29 2 30.7 25 -2.8 25 -4.8 7 126 Sengenarit, D, 2016 ¹⁰ 25 -5.8 126.2 25 -4.8 7 126 Sengenarit, D, 2016 ¹⁰ 25 -5.8 126.2 25 -4.7 126 Sengenarit, D, 200, P, 0.00%, P, 0.00%, P = 0.00% 16 0.00% 16 16 16 Teter OP, e, Q(-3 U 3 athyroid hormone (pg/ D 1.8 1 1.2 1 1.2 1 1.2 1 1.2 1 1.4 1 1.2	Mean Diff. with 95% Cl 36.70 [-109.30, 142 53.10 [-63.94, 170 19.70 [-61.315, 852 -2.00 [-72.79, 68 16.87 [-38.91, 72 28.70 [-98.87, 156 2.90 [-67.25, 73 8.89 [-52.58, 70	Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68 36]
$\label{eq:response} \begin{array}{l} \text{Random-Hetchs FRML}\\ \text{Rendom-Hetchs}, \text{Mathematical}, Math$	model Ost-Introventional Treatment C N Mean SD N 4 20.87 70.2 25 5 20.05 82.7 20 15 15 34.7 12.7 25 3- P = 0.005, H = 1.00 8, p = 0.80 10 11 15 34.7 12.7 25 3- P = 0.005, H = 1.00 8, p = 0.80 10 11 41 16.13 214.3 25 11 15 347.7 128.2 25 3- P = 0.005, H = 1.00 8, p = 0.54 10 11	Lintact parathyroid hormon Control 227 208.8 125 693.2 84.4 126.7 - 97.6 241 45.4 126.9 - 0 0 0 0 0 0 0 0 0 0 0 0 0	e (pg/ml) Mean Diff. with 95% C1 -0.8.30 (174.00) 0.760 (256.4, 204.44) 1.8.00 (256.4, 256.4) 1.8.28 (-375.0, 74.07) 18.28 (-375.0, 74.07) -36.50 (169.87, 91.27) -36.50 (169.87, 91.27) -36	Weight (%) 12.46 0.32 34.05 10.49 34.68	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	-3 U 3 athyroid hormone (pg/s D 1.8 1 1.2 1 1.2 - 1 1.2 - 1 1.3 1 1.4 1	Mean Diff. with 95% CI 38.70 [-109.30, 182 53.10 [-8.34, 170 19.70 [-81.51, 82 -2.00 [-7.27, 8 2.8.70 [-98.87, 156 2.90 [-67.25, 73 8.89 [-52.58, 70 13.27 [-28.04, 54	Weight (%) 70) 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68 36] 58]
$\begin{array}{c} \text{Random-Refects FRML } \\ \text{Random-Refects FRML } \\ \text{Study} \\ \text{Study} \\ \text{After trial Sampani, D. 2016^{(22)}} \\ \text{Study} \\ \text{Mater trial Sampani, D. 2018^{(22)}} \\ \text{Sampani, D. 2018^{(22)}} \\ Sam$	Model Ost-Introvention N Mean 50 100.2 51 100.3 94 200.5 100.3 94 101.5 347.1 103.3 90.005, H° = 1.00 9, p = 0.60 14 153 347.1 163.2 174.0 163.3 18.7 9.8, p = 0.54 14 14.9 16.9 18.0 18.0 18.0 18.0 18.0 19.0005, H° = 1.00 48.0 10.0016, H° = 1.00 48.0	Lintact parathyroid hormon Jonnol 227 208.8 	e (pg/ml) Meen Diff. with 85% Cl 28.30 [-174.30, 117.70] 87.40 [-28.44, 29.44] 4.30 [-48.49, 75.09] 18.29 [-37.50, 74.07] -36.30 [-163.87, 91.27] 3.30 [-66.85, 78.48] -1.29 [-62.76, 60.19] 9.45 [-31.87, 50.76]	Weight (%) 12.46 0.32 34.05 10.49 34.68	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	-3 U 3 athyroid hormone (pg/s b 10 10 12 12 12 13 14 14 1 15 15 1 1 1 1 1 1 1 1 1 1 1 1 1	Mean Diff. Mean Diff. with 95% Ci 36.70 [-109.30, 162 53.10 [-43.34, 7] 19.70 [-43.15, 622 53.10 [-43.34, 7] 19.70 [-43.47, 156 19.70 [-48.47, 156 2.20 [-47.27, 7] 28.89 [-42.58, 7] 13.27 [-48.04, 54	Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68 36] 58]
$\label{eq:source} \begin{array}{c} \text{Random-Refacts REMA}\\ Source by:$	Model Treatment Treatment Maxen 50 Maxen 50 1 702.2 50 20.6 1 503.5 1 503.5 1 503.5 1 503.5 9, p = 0.60 14 101.3 15 347.7 18.7 726.2 19. p = 0.60 14. 101.3 15. 347.7 16.3 214.3 16.3 214.3 16.3 214.3 16.3 9.0 16.9 9.0 17. 9.000%, H" = 1.00 8, p = 0.78 10.0 12. 9.0.04	Intact parathyroid hormon amen 50 227 208.8 323 182.6 334 128.7 4 57.6 241 4 57.6 241 4 57.6 241 57.6 25.6 25.6 25.6 25.6 25.6 25.6 25.6 25	e (pg/ml) Mean Diff. with 15% Cl 28.30 [174.30, 117.70] 87.40 [2544, 204.40] 18.20 [73.88, 713.88] 4.30 [46.49, 75.09] 18.22 [-37.50, 74.07] -30.50 [163.87, 91.27] 3.30 [-40.85, 79.46] -1.29 [-42.76, 60.19] 9.45 [-31.67, 50.76] 200	Weight (%) 8.01 12.46 0.32 34.05 10.49 34.68	$ \begin{array}{c c c c c c c c c c c c c c c c c c c $	-3 U 3 athyroid hormone (pg/s D 18 1 18 1 18 1 18 1 19 1 19 1 19 1 10	mt) Mean Diff. with 95% C1 38.70[-109.30, 182 38.70[-103.18, 82 -2.00[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-62.58, 70 18.87] (-38.87, 166 2.30[-67.55, 73 8.89] (-52.56, 70 13.27[-28.04, 54	Weight (%) 70] 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68 36] 58]
Random-effects FRML Souted by:	$\begin{array}{r} \mbox{model} \\ \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Lintact parathyroid hormon Common 237 208.8 332 1826 43.4 126.7 43.4 126.7 45.4 126.9 0 0 0 0 0 0 0 0 0 0 0 0 0	e (pg/ml) Mean Dif. with 65% Cl 48.60 [174.30, 117.70] 87.40 [25.64, 20.44, 4.50 [25.64, 20.44, 4.50 [25.65, 71.48] 4.50 [46.87, 75.09] 18.29 [47.75, 75.09] 18.29 [47.75, 77.60] 9.45 [-31.87, 50.76] 9.45 [-31.87, 50.76]	Weight (%) 8.01 12.46 0.32 34.05	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	-3 U 3 athyroid hormone (pg/n 	mt)) Mean Diff. with 95% C1 38.70[-109.30, 182 38.10[-43.54, 170 170]-413.15, 852 -2.00[-72.79, 68 16.87[-38.87, 172 28.70[-68.87, 159 2.20[-47.25, 73 8.89[-42.56, 70 13.27[-28.04, 54 0	Weight (%) 70) 8.01 14] 12.46 55] 0.32 79] 34.05 66] 27] 10.49 05] 34.68 36] 58]
Random-effects FRML Souted by:meta_i_d Subdy After trial Sampanit, D. 2019 ²²² ; Darke, P. 2020 ¹²⁰ ; Bian, Z. 2021 ⁶⁰ ; Bian, Z. 2021	model Transmert Mean 0.0 Value 0.0 N M 40.00.7 302.2 50.200.6 262.7 103.5 94.0 115 34.7 115 34.7 115 34.7 115 34.7 116.3 214.3 12 2.4 14 10.12 15 354.7 16.2 2.5 17 -0.00%, H= 1.00 18, p = 0.78 12 Q(1) = 0.21, p = 0.64	Lintact parathyroid hormon Control 227 208.8 43.4 126.7 43.4 126.7 45.4 126.7 45.4 126.9 6 -1000 500 6 500 1	e (pg/ml) Mean Dif. with 80%C 28.30 [174.30, 117.70] 87.80 [2564, 2044] 4.30 [-66.49, 75.09] 18.29 [-37.50, 74.67] -36.30 [168.87, 91.27] 0.30 [-66.85, 79.46] -1.29 [-42.76, 60.19] 9.45 [-31.87, 50.78]	Weight (%) 8.01 12.46 0.32 34.05	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	-3 U 3 athyroid hormone (pg/n 	ml) Mean Diff. with 955 02 38.70[-109.30, 182 35.10[-43.84, 170 19.70]-451.315, 852 20.1-72.79, 60 18.87[-38.87], 75 28.70[-49.87, 156 2.20[-472.35, 70] 4.8.99[-42.54, 70] 13.27[-28.04, 54] 5	Weight (%) 70] 8.01 14] 12.46 55] 0.32 70] 34.05 66] 34.68 36] 58]
$\label{eq:response} \begin{array}{c} \text{Random-effects FRML }\\ \text{Study} & \text{After trial }\\ \text{Study} & \text{After trial }\\ \text{Study} & \text{After trial }\\ \text{Study} & \text{Random}(D, D, 2018^{202})\\ \text{Standom}(D, 2018^{202})\\ S$	model Transmert Memor 0.0 Variation 0.0 Marcin 0.0 <t< td=""><td>Lintact parathyroid hormon Control 227 208.8 232 208.8 43.4 128.7 43.4 128.7 43.4 128.7 43.4 128.7 43.4 128.9 4 4 4 4 4 4 4 4 4 4 4 4 4</td><td>e (pg/ml) Mean Dif. with 95% C1 -28.30 [-174.30, 117.70] 87.40 [-28.44, 204.44] 4.00 [-78.48, 713.88] 4.00 [-78.48, 75.09] 18.29 [-37.50, 74.67] -3.05.30 [-163.87, 91.27] 9.30 [-06.85, 79.46] -1.29 [-32.76, 01.19] 9.45 [-31.87, 50.76] -200 -2</td><td>Weight (%) 8.01 12.46 34.05 10.49 34.68</td><td>$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$</td><td>-3 U 3 athyroid hormone (pg/ D </td><td>mt)) Mean Diff. with 95% CI 367.07 (-109.30, 182 35.10 (-403.31, 852 35.10 (-403.87, 156 35.10 (-403.87, 156 36.87 (-408.87, 156 36.87 (-408.87, 156 36.89 (-42.58, 70 13.27 (-28.04, 54)</td><td>Weight (%) 8.01 14 12.46 55 0.32 0.3666 34.68 366 568</td></t<>	Lintact parathyroid hormon Control 227 208.8 232 208.8 43.4 128.7 43.4 128.7 43.4 128.7 43.4 128.7 43.4 128.9 4 4 4 4 4 4 4 4 4 4 4 4 4	e (pg/ml) Mean Dif. with 95% C1 -28.30 [-174.30, 117.70] 87.40 [-28.44, 204.44] 4.00 [-78.48, 713.88] 4.00 [-78.48, 75.09] 18.29 [-37.50, 74.67] -3.05.30 [-163.87, 91.27] 9.30 [-06.85, 79.46] -1.29 [-32.76, 01.19] 9.45 [-31.87, 50.76] -200 -2	Weight (%) 8.01 12.46 34.05 10.49 34.68	$\begin{tabular}{ c c c c c c c c c c c c c c c c c c c$	-3 U 3 athyroid hormone (pg/ D 	mt)) Mean Diff. with 95% CI 367.07 (-109.30, 182 35.10 (-403.31, 852 35.10 (-403.87, 156 35.10 (-403.87, 156 36.87 (-408.87, 156 36.87 (-408.87, 156 36.89 (-42.58, 70 13.27 (-28.04, 54)	Weight (%) 8.01 14 12.46 55 0.32 0.3666 34.68 366 568
Rancton-effects FEML Study State by:	model Transmet Cost Mean 50 N Mann 50 N	Lintact parathyroid hormon Control 227 208.8 232 208.8 43.4 126.7 43.4 126.7 43.4 126.7 43.4 126.9 44.4 126.9 45.4 12	e (pg/ml) Mean Diff. with 95% C1 -28.30 [-174.30, 117.70] 87.40 [-264.30 4 47 -20.00 [758.86 713.88] 4.30 [-66.46 75.09] 18.22 [-37.50, 74.07] -3.6.30 [-163.87, 91.27] 9.30 [-66.85, 79.45] -1.22 [-62.76, 60.19] 9.45 [-31.87, 50.76] 0.45 [-31.87, 50.76]	Weight (%) 8.01 12.46 34.05 10.49 34.68	Bandom-effects REML model Change in intact par Treatment Change in intact par Treatment Change in intact par Treatment Control State of the second secon	-3 U 3 athyroid hormone (pg/) 	ml) Mean Diff. with 95% Cl 53.10[-4334, 170 19.70[-41315, 852 20.0[-72.78, 64 19.70[-48.87, 156 20.0[-72.78, 64 19.70[-48.87, 156 20.0[-72.78, 64 13.27[-28.04, 54 0] Mean Diff. C	Weight (%) 707 8.01 12.46 1141 12.45 0.32 1141 12.46 0.31 1141 12.47 10.49 1151 10.51 34.68 1151 10.49 10.51 1155 34.68 10.51 1151 10.49 10.51 1152 10.49 10.51 1152 10.49 10.51 1153 10.49 10.51 1153 10.49 10.51 1154 10.51 10.51 1154 10.51 10.51 1154 10.51 10.51 1155 10.51 10.51 1155 10.51 10.51 1155 10.51 10.51 1155 10.51 10.51 1155 10.51 10.51 1155 10.51 10.51 1155 10.51 10.51 1155 10.51 10.5
$\begin{array}{c} \text{Ranctore-Hetc's FRML } \\ \text{Study} \\ \text{Study} \\ \text{After trial } \\ \\ \text{Study} \\ \text{After trial } \\ \\ \text{Study} \\ \text{After trial } \\ \\ \\ \text{Study} \\ \text{Study} \\ \\ \\ \\ \text{Study} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$	Model Sost-interventional Ost-interventional 0 N Mean SD N M SD N M M SD N M M SD N M M SD N M M SD 202 20 M SD 10 11 SD N N M M SD 20.0 SD N M 161.3 214.3 25 11 SD SD 7.128.7 25 32 M 161.3 214.3 25 11 M Peo.000%, H* = 1.00 8, p = 0.54 10 Mean SD N M 100 odel Post-intervent N M N	Lintact parathyroid hormon Control 227 208.8	e (pg/ml) Mean Diff. with 95% Cl -28.30 [-174.30, 117.70] 87.40 [-264.30, 117.70] 87.40 [-264.40, 75.00] 18.20 [-46.40, 75.00] 9.45 [-31.87, 50.76] 000 000 Mean Diff. 1 Mean Diff. 1 000	Weight (%) 8.01 12.46 0.32 34.65 10.49 34.68	BANdom-effects REML model Change in intact par Treatment Change in intact par Treatment Control Statut Control Sampanit, D. 2016 ⁽²⁷⁾ 4, 17, 2016 ⁽²⁷⁾ 4, 17, 2016 ⁽²⁷⁾ 5, 2012 Control Sampanit, D. 2016 ⁽²⁷⁾ 5, 123, 2012 Control Sampanit, D. 2016 ⁽²⁷⁾ 5, 123, 2012 Control Sampanit, D. 2016 ⁽²⁷⁾ 5, 2012 Control Sampa	-3 U 3 athyroid hormone (pg/ 	ml) Mean Diff, with 95% C	Weight (%) 707 8.01 12.46 1141 12.45 0.32 1141 12.46 0.51 1155 0.32 0.34 1155 0.34 68 1155 34 68 1155 58 58 116 Weiglig (%)
$\label{eq:source} \begin{array}{c} \text{Random-Relects REML }\\ \textbf{Source by: meta_Jet}\\ \textbf{Source by: meta_Jet}\\ \textbf{Source Passed}\\ So$	model Sost-interventional 0 mean S0 N M M Mean S0 N M 44 20.87 30.2.2 25 16 20.0.6 20.2.7 51 15 34.7 128.7 25 9. p = 0.60 9. M M 24 161.3 214.3 25 11 15 34.7 128.7 25 3 9. p = 0.60 M 161.3 214.3 25 11 15 347.1 128.2 25 3 4 161.3 214.3 128.2 25 3 15 347.1 128.2 25 3 40.9 -0.00%, H ⁺ = 1.00 4 -0.20% 40.9 -0.00%, H ⁺ = 1.00 4 -0.01% odel N M -0.01% N Treatment C N M -0.01% N	lintact parathyroid hormon amini 227 208.8	e (pg/ml) Meen Diff. with 15% Cl -28.30 [-174.30, 117.70] 87.40 [-28.44, 20	Weight (%) 8.01 12.46 0.32 34.05 10.49 34.68 (%) 34.68	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	-3 U 3 athyroid hormone (pg/s 	ml) Mean Diff. with 95% C1 36.70[-109.30, 182 35.10[-43.54, 170 15.20]-43.15, 852 -2.00[-72.78, 68 2.200[-72.78, 68 2.200[-72.78, 68 2.200[-72.78, 68 2.200[-72.78, 68 2.200[-72.78, 68 2.200]-72.78, 68 2.200[-72.78, 78 2.200]-72.78, 78 2.200[-72.78, 78 2.200]-72.78, 78 2.200[-72.78, 78 2.200[-72.78, 78] 2.200[-72.78, 78] 2.200[Weight (%) Weight (%) (%) (%) (%) 0.32
$\label{eq:source} \begin{array}{c} \text{ReadCore-Refects FRML,}\\ Source by:$	model Post-Intervent N N Mean S0 N M 42 20.7 30.2 25 N M 44 20.8 30.2 25 N M 14 20.8 20.2 25 N M 15 34.7 128.7 25 N M 15 34.7 128.7 25 N M 15 34.7 128.7 25 N M 15 34.7 128.2 25 N M 16 0.24 14 10 N N N 16 12.4 N M N N N N 00.9 P 7.6 <td< td=""><td>lintact parathyroid hormon amini 227 208.8 227 208.8 228 208.2 228 208.2 227 208.8 229 208.8 229 208.8 229 208.8 220 208.8 200 200 200 200 200 200 200 200 200 200</td><td>e (pg/ml) Meen Diff. with 15% Cl -28.30 [174.30, 117.70] 87.40 [-28.4, 20.44] -30.50 [-318.87, 73.88] 4.30 [-64.49, 75.09] 18.23 [-37.50, 74.07] -30.50 [-46.49, 75.09] 18.23 [-37.50, 74.07] -30.50 [-46.49, 75.09] 9.45 [-31.87, 50.76] -30.50 [-40.45] 9.45 [-31.87, 50.76] -30.50 [-40.45] -30.50 [-40.45] -30.50 [-40.45] -30.50 [-40.45] -30.50 [-40.40, 0.29] -3.30 [-1.40, 4.00] -3.30 [-1.40, 4.00] -3.3</td><td>Weight (%) 8.01 12.46 0.32 34.05 34.68 10.49 34.68 (%) 31.55 36.48</td><td>$\begin{array}{c c c c c c c c c c c c c c c c c c c$</td><td>-3 U 3 athyroid hormone (pg/ </td><td>ml) Mean Diff. with 95% C1 36.70[-109.30, 182 35.10[-43.54, 107 10.70[-41.31, 682 -2.00[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72, 78 3.30]-72, 78 3.30]-72</td><td>Weight (%) Weight (%) 277 0.40 34.05 277 0.40 5.01 277 0.40 5.01 277 0.40 5.01 98 24.21 0.40 401 50.11 51</td></td<>	lintact parathyroid hormon amini 227 208.8 227 208.8 228 208.2 228 208.2 227 208.8 229 208.8 229 208.8 229 208.8 220 208.8 200 200 200 200 200 200 200 200 200 200	e (pg/ml) Meen Diff. with 15% Cl -28.30 [174.30, 117.70] 87.40 [-28.4, 20.44] -30.50 [-318.87, 73.88] 4.30 [-64.49, 75.09] 18.23 [-37.50, 74.07] -30.50 [-46.49, 75.09] 18.23 [-37.50, 74.07] -30.50 [-46.49, 75.09] 9.45 [-31.87, 50.76] -30.50 [-40.45] 9.45 [-31.87, 50.76] -30.50 [-40.45] -30.50 [-40.45] -30.50 [-40.45] -30.50 [-40.45] -30.50 [-40.40, 0.29] -3.30 [-1.40, 4.00] -3.30 [-1.40, 4.00] -3.3	Weight (%) 8.01 12.46 0.32 34.05 34.68 10.49 34.68 (%) 31.55 36.48	$\begin{array}{c c c c c c c c c c c c c c c c c c c $	-3 U 3 athyroid hormone (pg/ 	ml) Mean Diff. with 95% C1 36.70[-109.30, 182 35.10[-43.54, 107 10.70[-41.31, 682 -2.00[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72.78, 78 3.30]-72, 78 3.30]-72, 78 3.30]-72	Weight (%) Weight (%) 277 0.40 34.05 277 0.40 5.01 277 0.40 5.01 277 0.40 5.01 98 24.21 0.40 401 50.11 51
$\begin{array}{r} \text{Random-Refects FRML } \\ \text{Random-Refects RFML } \\ \text{Study} \\ \text{Study} \\ \text{After trial } \\ \text{Saregnani, D. 2018}^{272} \\ \text{Djurk, P. 2002} \\ Random Reference in the state of the$	model Treatment Treatment Maxen S0 Maxen S1 Maxen S1 Maxen S1 Maxen S2 Maxen S0 Maxen S0 Maxen S0 Maxen S2 <td>lintact parathyroid hormon common 227 208.8 227 208.8 228 208.2 227 208.8 4 227 208.8 4 227 208.8 4 227 208.8 4 4 227 208.8 4 4 4 4 4 4 4 128.9 4 4 4 4 4 128.9 4 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 4 4 128.9 4 4 4 4 4 4 4 4 4 4 4 4 4</td> <td>e (pg/ml) Mean Diff. with 1955 Cl -28.30 [172.430, 117.70] 87.40 [25.44, 20.440] 4.30 [-64.49, 75.09] 18.29 [-37.50, 74.67] -30.50 [-158.87, 79.45] -30.50 [-168.87, 79.45] -3.50 [-40.55, 79.45] 9.45 [-31.87, 50.76] -3.60 [-74.91, 0.29] -3.650 [-7.49, 0.29] -3.054 [-5.73, 3.84]</td> <td>Weight (%) 12.46 0.32 34.68 34.68 Weight (%) 31.55 36.48</td> <td>Bandom-effects REML model Change in intact par Treatment Change in intact par Treatment Bangpanit, D. 2014⁰²⁰, 54 47 302.2 25 10.3 200 PMC More, P. 2020⁰²⁰, 56 72.1 82.7 29 19 62.7 More, P. 2020⁰²⁰, 55 72.1 82.7 29 19 10 Mar, Z. 2021⁰⁴⁰, 15 52.6 94.8 10 205.3 903 Mar, 2. 2021⁰⁴⁰, 15 25 12.8 12.8 72.7 25 13.1 12.8 Mar, 2. 2021⁰⁴⁰, 25 12.8</td> <td>-3 0 3 athyroid hormone (pg/ b b b c c c c c c c c c c c c c c c c</td> <td>ml) Mean Diff. with 95% Cl 38.70[-109.30, 182 53.10[-43.5, 85 -2.00]-72.78, 68 68.87[-48.87, 169 2.30[-47.25, 73 8.89[-42.58, 70 13.27[-28.04, 54) Mean Diff. Mean Diff. -0.30[-3.00, 2 0.39[-1.84, 2</td> <td>Weight (%) (%) (%) 701 8.01 8.141 12.46 551 0.32 701 34.05 9051 34.06 8691 (%) 8693 (%) 8694 24.22 8695 24.22 8691 50.16 611 50.16</td>	lintact parathyroid hormon common 227 208.8 227 208.8 228 208.2 227 208.8 4 227 208.8 4 227 208.8 4 227 208.8 4 4 227 208.8 4 4 4 4 4 4 4 128.9 4 4 4 4 4 128.9 4 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 128.9 4 4 4 4 4 128.9 4 4 4 4 4 4 4 4 4 4 4 4 4	e (pg/ml) Mean Diff. with 1955 Cl -28.30 [172.430, 117.70] 87.40 [25.44, 20.440] 4.30 [-64.49, 75.09] 18.29 [-37.50, 74.67] -30.50 [-158.87, 79.45] -30.50 [-168.87, 79.45] -3.50 [-40.55, 79.45] 9.45 [-31.87, 50.76] -3.60 [-74.91, 0.29] -3.650 [-7.49, 0.29] -3.054 [-5.73, 3.84]	Weight (%) 12.46 0.32 34.68 34.68 Weight (%) 31.55 36.48	Bandom-effects REML model Change in intact par Treatment Change in intact par Treatment Bangpanit, D. 2014 ⁰²⁰ , 54 47 302.2 25 10.3 200 PMC More, P. 2020 ⁰²⁰ , 56 72.1 82.7 29 19 62.7 More, P. 2020 ⁰²⁰ , 55 72.1 82.7 29 19 10 Mar, Z. 2021 ⁰⁴⁰ , 15 52.6 94.8 10 205.3 903 Mar, 2. 2021 ⁰⁴⁰ , 15 25 12.8 12.8 72.7 25 13.1 12.8 Mar, 2. 2021 ⁰⁴⁰ , 25 12.8	-3 0 3 athyroid hormone (pg/ b b b c c c c c c c c c c c c c c c c	ml) Mean Diff. with 95% Cl 38.70[-109.30, 182 53.10[-43.5, 85 -2.00]-72.78, 68 68.87[-48.87, 169 2.30[-47.25, 73 8.89[-42.58, 70 13.27[-28.04, 54) Mean Diff. Mean Diff. -0.30[-3.00, 2 0.39[-1.84, 2	Weight (%) (%) (%) 701 8.01 8.141 12.46 551 0.32 701 34.05 9051 34.06 8691 (%) 8693 (%) 8694 24.22 8695 24.22 8691 50.16 611 50.16
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$\label{eq:expectation} \begin{array}{c} \text{Reactor-releteds FEMLs}\\ \text{Reactor-releted by:} & \text{Reactor-releted by}\\ \text{Study} & \text{After trial}\\ \text{Samparit, D. 2008}^{(27)} & \text{Study} \\ \text{Mater trial} & \text{Samparit, D. 2018}^{(27)} & \text{Samparit, D. 2018}^{(27)} \\ \text{Reactor-Reactor-releted by} & \text{Reactor-releted by} \\ \text{Reactor-Reactor-releted by} & \text{Reactor-releted by} \\ \text{Reactor-releted by} & \text{Reactor-releted by} \\ Re$	model Treatment C Name 50 Maxe 50 N Maxe 10 202.7 10 202.7 10 202.7 11 53 15 347.7 15 354.7 16.13 214.3 15 364.7 16.2 21.4 16.3 94.9 16.3 94.9 16.3 94.9 16.3 94.9 16.3 94.9 16.3 94.9 16.3 94.9 16.3 94.9 16.3 94.9 17 24 16.6 25 15 12.4 15 12.4 12 12.6 12 12.4 12 12.6 12 12.4 13.4 11.9 14.1 10 <	Lintact parathyroid hormon Control 227 208.8 227 208.8 43.4 126.7 43.4 12	e (pg/ml) Mean Diff. with 95% Cl -28.30 [174.30, 117.70] 87.80 [-264.50 A45 14.00 [738.85, 713.84] 4.00 [738.85, 713.84] -1.29 [-42.76, 60.19] 9.45 [-31.87, 50.78] 9.45 [-31.87, 50.78] 0.45	Weight (%) 12.46 34.05 10.49 34.68 10.49 34.68 10.49 34.68	Bandom-effects REML model Change in intact part Change in intact part Not intact part State ment Control State ment Control State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment State ment Control State ment Notice Notice Notice Notice State ment Notice	-3 U 3 athyroid hormone (pg/h - - - - - - - - - - - - -	ml) Mean Diff. with 95% C1 38.70[-109.30, 183 35.10[-33.4, 170 19.70]-413.15, 592 20.0[-72.78, 60 18.87[-38.87], 72 28.70[-98.87, 156 20.0[-72.78, 60 13.27[-38.84]-42.58, 70 13.27[-38.04, 54 0) Mean Diff. 0 -0.30[-3.00, 2 0.39[-1.84, 2 -0.40[-4.19, 3] -0.40[-4.19, 3]	Weight (%) Weight (%) 70 8.01 8.11 12.46 93 0.32 93 34.68 93 34.68 94 94.68 95 34.68 96 34.68 96 34.68 97 10.49 98 24.22 401 50.11 61] 39
$\begin{array}{c} \text{Ranctom-effects FRAM.}\\ Render affects and the second $	$\begin{array}{r} \mbox{model} \\ \hline \begin{tabular}{lllllllllllllllllllllllllllllllllll$	Lintact parathyroid hormon Control 227 208.8 227 208.8 43.4 126.7 43.4 126.7 43.4 126.7 43.4 126.7 43.4 126.7 43.4 126.7 43.4 126.7 44.4 126.7 45.5 241 5.5 241 5.5 5.0 5.0 1 5.5 5.0 5.5 5.0 5	e (pg/ml) Mean Diff. with 95% C1 -28.30 174.30, 117.70] 87.40 25.44, 20.44 14.00 738.85, 713.83 4.00 738.85, 713.83 4.00 738.85, 713.83 4.00 64.89, 75.09 18.29 42.76, 60.19] 9.45 -31.87, 50.76] 9.45 -31.87, 50.76] 0.45 -31.87, 50.76] 0.45 -31.87, 50.76] 0.45 -31.87, 50.76] 0.45 -31.87, 50.76] -3.60 7.40, 0.29] -1.30 1.40, 4.00] -0.34 5.73, 3.84] -5.80 -9.59, -2.01] -5.80 -9.59, -2.01]	Weight (%) 8.01 12.46 0.32 34.05 10.49 34.68 10.49 34.68 34.68 34.68		-3 0 3 athyroid hormone (pg/h - - - - - - - - - - - - -	ml) Mean Diff. with 95% C1 36.70[-109.30, 183 53.10[-43.54, 170 19.70[-413.15, 852 20.0[-72.78, 64 18.87[-38.87], 75 28.70[-48.87, 156 20.0[-72.78, 64 18.87[-42.83, 70 13.27[-28.04, 54 13.27[-28.04, 54 0 13.27[-28.04, 54 0 0 13.27[-28.04, 54 0 0 13.27[-28.04, 54 0 0 0 0 0 0 0 0 0 0 0 0 0	Weight (%) Weight (%) 70 8.01 8.05 0.32 9.34.68 0.32 869 34.68 9.36 34.68 9.36 34.68 9.36 34.68 669 34.68 669 24.22 401 50.14 671 391 392 25.55
Random-Refects REML Southed by:metadist Southed by:metadist Southed by:metadist Southed by:metadist Southed Dist netadist Southed Dist netadist During trail Bian, Z. 2021 ^(R) : Bian, Z. 202		Lintact parathyroid hormon Jonitol 127 208.8 227 208.8 228 208.2 228 208.2 227 208.8 228 208.2 228 208.2 228 208.2 229 208.8 229 208.8 229 208.8 229 208.8 229 208.8 220 208.8 200 200 200 200 200 200 200 200 200 200	e (pg/ml) Meen Diff. with 85% Cl -28.30 [-174.30, 117.70] 87.40 [-28.44, 20.44, -30.0 [-76.88, 71.38.8] 4.30 [-46.49, 75.09] 18.20 [-46.49, 75.09] 18.20 [-46.49, 75.09] 18.20 [-46.49, 75.09] 18.20 [-46.49, 75.09] 9.45 [-31.87, 50.76] 9.45 [-31.87, 50.76] 9.45 [-31.87, 50.76] 0.45 [-31.87, 50.7	Weight (%) 8.01 12.46 34.05 10.49 34.68 10.49 34.68 34.68 31.55 36.48 31.97	Andom-effects REML model order by:meta3 Cance in intact par Teamment F Cance in intact par Teamment Control 0 N Bady N Mean 50 N Mean S0 Status N Mean 50 N Mean S0 N Status N N S0 N Mean S0 N Status N S0 N Mean S0 N Mean S1 S1 <ths1< th=""> S1 <ths1< th=""></ths1<></ths1<>	-3 0 3 athyroid hormone (pg/ 	ml) Mean Diff. with 95% C1 36.70[-109.30, 182 53.10[-43.54, 173 18.70[-413.15, 852 200[-72.78, 64 18.70[-48.87, 156 200[-72.78, 64 18.70[-48.87, 156 200[-72.78, 64 13.27[-28.04, 54 13.27[-28.04, 54 13.27[-28.04, 54 0 0 13.27[-28.04, 54 0 0 13.27[-28.04, 54 0 0 0 0 1.20[-2.29, 5 0 0 0 0 0 0 0 0 0 0 0 0 0	Weight (%) Weight (%) 70 8.01 114 12.46 551 0.32 0.30 34.68 27 10.49 360 34.68 Weight (%) 40.50 669 24.22 669 24.23 301 25.55
$\label{eq:source} \begin{split} & Random-Relacks REML, so source by:meta, all so source b$		lintact parathyroid hormon amini 227 208.8 • 232 182.6 • 44 128.7 • 57.6 241 • 45.4 128.9 • -1000 -500 • 500 1 tional 25-hydroxyvitamin D2 ontrol Mean 50 23.2 7.8 • 1.1 2.8 • 25.8 8.9 • 53	e (pg/ml) Meen Diff. with 15% Cl 28.30 [-174.30, 117.70] 87.40 [-28.44, 20.	Weight (%) 8.01 12.46 34.05 34.68 34.68 Weight (%) 31.55 36.48 31.97	Bandom-effects REML model Change in intact par Treatment Change in intact par Treatment Change in intact par Treatment Change in intact par Num, 2002 ⁽²⁰⁾ 2000 ⁽²⁰⁾ 27, 120, 22, 25, 10, 3, 000 (300, c, P. 2002 ⁽²⁰⁾) 2001 ⁽²⁰⁾ 27, 120, 22, 72, 91, 19, 103, 200 (300, c, P. 2002 ⁽²⁰⁾) 2001 ⁽²⁰⁾ 27, 120, 22, 72, 91, 19, 103, 200 (20, 12, 120, 200, 120, 200, 120, 200, 120, 200, 100, 200, 100, 200, 100, 200, 100, 1	-3 0 3 athyroid hormone (pg/ 	ml) Mean Diff. with 95% C1 36.70[-109.30, 182 35.10[-33.44, 70] 36.70[-43.16, 86] -2.20[-72.78, 68] 2.20[-72.78,	Weight (%) Weight (%) 70 8.01 11 12.46 9 0.405 938 34.65 939 34.65 94.05 34.68 969 24.22 661 39 393 25.55
$\begin{array}{r} \text{Random-Relects REM.}\\ \text{Souted by:meta_i_d}\\ \hline \textbf{E} & \textbf{S}_{int}\\ \text{Souted by:meta_i_d}\\ \text{Sangpani, D. 2016^{(2)}}\\ \text{Que, P. 2202^{(2)}}\\ \text{Que, P. 2202^{(2)}}\\ \text{Que, P. 2202^{(2)}}\\ \text{Ban, Z. 202^{(4)}}\\ \text{Za02^{(4)}}\\ Za02^{$		Lintact parathyroid hormon amini 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 228 208.2 227 208.8 229 208.8 229 208.8 229 208.8 229 208.8 220 208.8 200 200 200 200 200 200 200 200 200 200	e (pg/ml) Mean Diff. with 15% Cl -28.30 [174.30, 117.70] 87.40 [28.44, 29.44] 4.30 [46.49, 75.09] 18.23 [-37.50, 74.07] -30.50 [-168.87, 91.27] 9.30 [-60.85, 79.48] -1.29 [-42.76, 60.19] 9.45 [-31.87, 50.76] -30.50 [-40.40, 20.30] -3.50 [-7.49, 0.29] 1.30 [1.40, 4.00] -0.34 [-57.3, 3.84] -5.80 [-6.59, -2.01] -5.80 [-6.59, -2.01] -2.52 [-6.79, 1.76]	Weight (%) 8.01 12.46 34.05 34.68 34.68 34.68 34.68 31.55 36.48 31.97	Bendin-effects REML model Change in intact par Treatment Staty: meta_dist Change in intact par Treatment Staty: meta_dist Nearming to Control Baengeanti, D. 2016 ⁰² , 4 Staty: meta_dist Colspan="2">Staty: meta_dist Colspan="2">Staty: meta_dist Colspan="2">Staty: meta_dist Colspan="2">Colspan="2" Colspan= 200%; H ^a = 1.00 Treatment Control Control Staty meta_dist Control Control Control Control Control Control Control	-3 0 3 athyroid hormone (pg/ 	ml) Mean Diff. with 95% C1 38.70[-109.30, 182 38.10[-43.18, 80 2.200[-72.78, 68 2.200[-72.78, 68 2.200]-72.78, 68 2.200[-72.78, 78 2.200]-72.78, 68 2.200[-72.78, 78 2.200]-72.78, 78 2.200[-72.78, 78 2.200[-72.78, 78] 2.200[-72.78, 78	Weight (%) Weight (%) 70 8.01 14 12.46 707 34.05 707 34.05 707 34.05 707 34.05 707 34.05 869 24.22 706 50.16 309 25.55 309 25.55
$\begin{array}{c} \text{Random-Relects REM.}\\ \text{Souted by:metadef}\\ \hline \textbf{B}_{add} & \textbf{B}_{add} & \textbf{B}_{add} & \textbf{B}_{add} \\ \hline \textbf{S}_{add} & \textbf{B}_{add} & \textbf{B}_{add} & \textbf{B}_{add} \\ \hline \textbf{S}_{add} & \textbf{B}_{add} & \textbf{B}_{add} & \textbf{B}_{add} & \textbf{B}_{add} \\ \hline \textbf{D}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} & \textbf{C}_{add} \\ \hline \textbf{B}_{add} & \textbf{C}_{add} \\ \hline \textbf{C}_{add} & \textbf{C}_{add} &$	Model Post-Interventional N Massin S0 N M 41 20.6.7 90.2.2 25 15 15 34.7 128.7 25 11 15 34.7 128.7 25 14 15 34.7 128.7 25 3 9, p = 0.60 4 161.3 214.3 25 11 15 34.7 128.2 25 3 4 161.3 214.3 128.2 25 3 15 34.7 128.2 25 3 16 12.4 14 10 6 25 17 12.4 1.0 10 10 10 0.9 $p = 0.00\%, H^{p} = 1.00$ 8 9 N N 16 12.4 4.1 10 10 10 10 0.0 $p = .7.6$ 0.5 15 12.4 4.1 10 11 <t< td=""><td>lintact parathyroid hormon amini 227 208.8 227 208.8 227 208.8 227 208.8 228 208.2 228 208.2 229 208.8 229 208.8 229 208.8 220 208.8 200 200 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0</td><td>e (pg/ml) Mean Diff. with 65% Cl 28.30 [172.430, 117.70] 87.40 [2564, 2344, 37.438] 4.30 [-64.49, 75.09] 18.23 [-37.50, 74.07] 3.30 [-65.87, 74.67] 3.30 [-65.87, 74.67] 3.30 [-65.87, 74.67] 9.45 [-31.67, 50.76] 0.00 3(ng/ml) Mean Diff. -3.550 [-7.49, 0.29] -3.550 [-6.59, -2.01] -5.580 [-6.59, -2.01] -5.580 [-6.59, -2.01] -5.580 [-6.59, -2.01] -2.52 [-6.79, 1.75]</td><td>Weight (%) 8.01 12.46 34.05 34.05 34.68 34.68 31.55 38.48 31.97</td><td>Berlin Ministry and Signature Change in intact par Treatment State in the second of the second</td><td>-3 0 3 athyroid hormone (pg/n </td><td>ml) Mean Diff. with 95% C1 38.70[-109.30, 182 38.10[-43.18, 82 -2.00]-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]</td><td>Weight (%) Weight (%) 70 8.01 14 12.46 27 10.49 28 34.65 39 34.68 66 34.68 67 44.62 68 24.22 40 50.16 61 30.9 25.52 53.9 10 10</td></t<>	lintact parathyroid hormon amini 227 208.8 227 208.8 227 208.8 227 208.8 228 208.2 228 208.2 229 208.8 229 208.8 229 208.8 220 208.8 200 200 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0 0	e (pg/ml) Mean Diff. with 65% Cl 28.30 [172.430, 117.70] 87.40 [2564, 2344, 37.438] 4.30 [-64.49, 75.09] 18.23 [-37.50, 74.07] 3.30 [-65.87, 74.67] 3.30 [-65.87, 74.67] 3.30 [-65.87, 74.67] 9.45 [-31.67, 50.76] 0.00 3(ng/ml) Mean Diff. -3.550 [-7.49, 0.29] -3.550 [-6.59, -2.01] -5.580 [-6.59, -2.01] -5.580 [-6.59, -2.01] -5.580 [-6.59, -2.01] -2.52 [-6.79, 1.75]	Weight (%) 8.01 12.46 34.05 34.05 34.68 34.68 31.55 38.48 31.97	Berlin Ministry and Signature Change in intact par Treatment State in the second of the second	-3 0 3 athyroid hormone (pg/n 	ml) Mean Diff. with 95% C1 38.70[-109.30, 182 38.10[-43.18, 82 -2.00]-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 68 2.30[-72.78, 68 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]-72.78, 78 2.30]	Weight (%) Weight (%) 70 8.01 14 12.46 27 10.49 28 34.65 39 34.68 66 34.68 67 44.62 68 24.22 40 50.16 61 30.9 25.52 53.9 10 10
$\begin{array}{r} \text{Random-effects REML } \\ \text{Random-effects REML } \\ \textbf{Southor by:metal_d} \\ \hline \textbf{Southor by:metal_d} \\ \hline \textbf{Southor by:metal_d} \\ \\ \text{Southor by:southor boxed } \\ \\ \text{Southor by:southor boxed } \\ \\ \text{Southor by:southor boxed } \\ \\ \text{After trial } \\ \\ \text{Southor boxed } \\ \\ \text{Southor boxed } \\ \\ \\ \text{More trial } \\ \\ \\ \text{Southor boxed } \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $	model Treatment Treatment Treatment Treatment Treatment Treatment M M M M M Treatment S 3 M Treatment C Post-intervent Treatment C M M M M M Treatment C M M M M M M M M M M M M M M M M M M M <th colspan="2</td> <td>Lintact parathyroid hormon control 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 2010 20</td> <td>e (pg/ml) Mean Diff. with 95% CI 28.30 [174.30, 117.70] 87.40 [25.44, 23.44] 4.30 [-64.49, 75.09] 18.29 [-37.50, 74.67] 9.30 [-40.85, 73.48] -1.29 [-42.76, 60.19] 9.45 [-31.87, 50.76] 000 3 (ng/ml) Mean Diff. -3.80 [-7.49, 0.29] - 1.30 [1-40, 4.00] - 0.34 [-5.73, 3.84] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.81 [-8.59, -2.01] -5</td> <td>Weight (%) 12.46 34.05 10.49 34.68 34.68 31.55 36.48 31.97</td> <td>Bandom-effects REML model order by:metadid Change in intact par meta_did Suby: Change in intact par meta_did Normality in the second of the</td> <td>-3 0 3 athyroid hormone (pg/n </td> <td>mi) Mean Diff. with 95% C1 38.70[-109.30, 182 53.10[-43.54, 170 170]-43.15, 852 -2.00[-72.79, 68 16.87[-38.87, 159 2.20[-472.55, 172 2.20]-472.55, 172 2.210[-472.55, 172 -2.20]-472.55, 172 -2.20]-42.55, 172 -2.20]-42.</td> <td>Weight (%) Weight (%) 70 8.01 114 12.46 50 0.32 739 34.05 340 34.68 869 34.68 669 24.22 401 50.16 399 25.52 100 10</td>	Lintact parathyroid hormon control 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 227 208.8 2010 20	e (pg/ml) Mean Diff. with 95% CI 28.30 [174.30, 117.70] 87.40 [25.44, 23.44] 4.30 [-64.49, 75.09] 18.29 [-37.50, 74.67] 9.30 [-40.85, 73.48] -1.29 [-42.76, 60.19] 9.45 [-31.87, 50.76] 000 3 (ng/ml) Mean Diff. -3.80 [-7.49, 0.29] - 1.30 [1-40, 4.00] - 0.34 [-5.73, 3.84] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.80 [-8.59, -2.01] -5.81 [-8.59, -2.01] -5	Weight (%) 12.46 34.05 10.49 34.68 34.68 31.55 36.48 31.97	Bandom-effects REML model order by:metadid Change in intact par meta_did Suby: Change in intact par meta_did Normality in the second of the	-3 0 3 athyroid hormone (pg/n 	mi) Mean Diff. with 95% C1 38.70[-109.30, 182 53.10[-43.54, 170 170]-43.15, 852 -2.00[-72.79, 68 16.87[-38.87, 159 2.20[-472.55, 172 2.20]-472.55, 172 2.210[-472.55, 172 -2.20]-472.55, 172 -2.20]-42.55, 172 -2.20]-42.	Weight (%) Weight (%) 70 8.01 114 12.46 50 0.32 739 34.05 340 34.68 869 34.68 669 24.22 401 50.16 399 25.52 100 10

FIGURE 4: Meta-analysis of the effect of STS on CKD-MBD parameters in patients with VC. Calcium, phosphate and iPTH were comparable between the STS group and the control group there were no significant changes in these parameters during and after the trials (A-F). During the trials, the mean level of 25(OH)VitD3 in the STS group was less than that of the controls (49 participants, MD: -5.80 ng/mL, 95% CI: -9.59 to -2.01 ng/mL), but no difference was noticed in the change during the trials between the two groups (G and H).

^	Post-interventional Serum So	dium (mmol/l)	Change in Serum Sodium (mmol/l)
Study	Treatment Control N Mean SD N Mean SD	Mean Diff. Weig with 95% CI (%)	ht Treatment Control Mean Diff. Weight Study N Mean SD N Mean SD with 95% CI (%)
After trial	26 137 2 0 20 199 5 0	0.50 / 0.62 (62) (62	After trial
Heterogeneity: $\tau^2 = 0$. Test of $\theta_i = \theta_j$: Q(0) =	20 137 2.9 29 130.5 2 .00, P = .%, H ² = .	0.50 [-0.83, 1.83]	$\label{eq:rescaled} \begin{array}{c} & 0 & 0 & 0 \\ \text{Heterogonality: } \tau^2 = 0.00, \ F = .%, \ F = . \\ & 0 & 0 & [-1.73, \ 0.93] \\ & \text{Test of } \theta_i = \theta_i^2 Q(0) = 0.00, \ p = . \end{array}$
During trial	24 1377 33 25 1376 3	0.10[-1.67, 1.87] 36.1	During trial
Heterogeneity: $\tau^2 = 0$. Test of $\theta_i = \theta_j$: Q(0) =	.00, I ² = .%, H ² = . 0.00, p = .	0.10 [-1.67, 1.87]	$\label{eq:constraint} \begin{array}{c} -3 & -3 & -3 & -3 & -3 & -3 & -3 & -3 $
Overall Heterogeneity: $\tau^2 = 0$. Test of $\theta_i = \theta_j$: Q(1) =	.00, l² = 0.00%, H² = 1.00 0.13, p = 0.72	0.36 [-0.71, 1.42]	Overail 0.05 [-1.09, 1 = 11.45%, H ² = 1.13 Hoterogeneity: t ² = 0.08, P = 11.45%, H ² = 1.13 0.05 [-1.09, 1.19]
Test of group differen	ces: Q ₆ (1) = 0.13, p = 0.72	0 1 2	Test of group differences: $Q_b(1) = 1.13$, $p = 0.29$
Random-effects REML Sorted by: _meta_id	model		-2 0 2 4 Random-effects REML model
С	Post-interventional Serum Po	tassium (mmol/l)	Sorted by: _meta_id Change in Serum Potassium (mmol/l)
Study	Treatment Control N Mean SD N Mean SD	Mean Diff. Weig with 95% Cl (%)	ht Treatment Control Mean Diff. Weight Study N. Mean SD N. Mean SD with 55% CI (%)
During trial	2) 24 57 0 25 55 0	0.20 (0.20 0.70) 100 0	During trial
Heterogeneity: $\tau^2 = 0$. Test of $\theta_i = \theta_j$: $Q(0) =$	24 0.7 .9 20 0.0 .9 .000, P = .%, H ² = .	0.20 [-0.30, 0.70]	Saengpanit, D. 2018 ⁽²⁷⁾ 24 . 5 . 9 . 25 . 2 . 9 . 0.30 [-0.20, 0.80] 100.00 Heterogeneity: r = 0.00, P = .%, H ² = . 0.30 [-0.20, 0.80] 0.00 − .
Overall		0.20 [-0.30, 0.70]	
Heterogeneity: $\tau^2 = 0$. Test of $\theta_i = \theta_j$: $Q(0) =$.00, I ² = .%, H ² = . -0.00, p = .		Overall 0.30 [-0.20, 0.80] Heterogeneity: τ² = 0.00, l² = .%, H² = . 0.30 [-0.20, 0.80]
Test of group differen	ces: Q ₆ (0) = -0.00, p = .		Test of $\theta_i = \theta_i$; Q(0) = 0.00, p = . Test of around differences: Q(0) = 0.00, p =
Random-effects REML Sorted by: meta id	5 0	.5 1	rest of group dimerences: $Q_{g}(0) = 0.00$, $p = .$
			Random-effects REML model Sorted by:meta_jd
E	Post-interventional Serum Chl	oride (mmol/l)	Change in Serum Chloride (mmol/l)
Study	Treatment Control N Mean SD N Mean SD	Mean Diff. Weig with 95% Cl (%	ght Treatment Control Mean Diff. Weight) Study N Mean SD N Mean SD with 95% CI (%)
After trial Djuric, P. 2020 (23)	26 102.1 3.5 29 102.8 3.3	-0.70 [-2.50, 1.10] 61.9	After trial ¹¹ Diuric, P. 2020 ⁽²³⁾ 266 3.5 29 .5 3.3
Heterogeneity: $\tau^2 = 0$ Test of $\theta_i = \theta_j$: Q(0) =	.000, I ² = .%, H ² = . -0.00, p = .	-0.70 [-2.50, 1.10]	Heterogeneity: $\tau^2 = 0.00$, $P = .$ Test of $\theta_i = \theta_i$: Q(0) = -0.00, $p = .$
During trial Saenopanit, D. 2018	22) 24 96.3 3.8 25 98.2 4.4	-1.90 [-4.20, 0.40] 38.0	During trial
Heterogeneity: $\tau^2 = 0$ Test of $\theta_i = \theta_j$: Q(0) =	.000, I ² = .%, H ² = . 0.00, p = .	-1.90 [-4.20, 0.40]	Saengpanit D. 2018 [™] 24 -6 3.8 25 .2 4.4 -0.80 [-3.10, 1.50] 38.09 Heterogeneity: r ⁴ = 0.00, l ² = .5%, l ² = . -0.80 [-3.10, 1.50] -0.80 [-3.10, 1.50] Test of 8 = 8; 2(Q) = -0.00, p = . -0.80 [-3.10, 1.50]
Overall Heteroceneity: x2 = 0	00 IZ = 0.00% HZ = 1.00	-1.16 [-2.58, 0.26]	Overall -0.99 [-2.40, 0.43]
Test of $\theta_i = \theta_j$: Q(1) =	0.65, p = 0.42		Heterogeneity: $\tau^2 = 0.00$, $ ^2 = 0.00\%$, $H^2 = 1.00$ Test of $B = B \cdot O(1) = 0.04$, $p = 0.84$
Test of group differen	ices: Q _p (1) = 0.65, p = 0.42	0 2	Test of group differences: $Q_{b}(1) = 0.04$, $p = 0.84$
Random-effects REML Sorted by: _meta_id	model		-4 -2 0 2
G	Post-interventional Serum Bicart	bonate (mmol/l)	Serier Hy:meta_id Change in Serum Bicarbonate (mmol/l)
	Treatment Control	Mean Diff. Weig	t Treatment Control Mean Diff. Weigh t Study N Mean SD With 95% CI (%)
After trial	N Mean SD N Mean SD	with 95% CI (%	After trial
Djuric, P. 2020 ⁽²³⁾ Yu, Y. 2016 ⁽²¹⁾	26 22 2.5 29 22 4 15 22.3 3.4 10 25.8 3		4 Djunc, P. 2020 264 2.5 29 0 4
Heterogeneity: $\tau^2 = 4$. Test of $\theta_i = \theta_j$: Q(1) =	.89, I² = 79.90%, H² = 4.97 4.97, p = 0.03	-1.62 [-5.05, 1.80]	Heterogeneity: $r^{2} = 0.77$, $F^{2} = 38.43\%$, $H^{2} = 1.62$ Test of $\theta_{i} = \theta_{i}^{2} Q(1) = 1.62$, $p = 0.20$
During trial Saengpanit, D. 2018	⁽²⁾ 24 20 .7 25 20.1 .7	-0.10 [-0.49, 0.29] 43.0	During trial
Heterogeneity: $\tau^2 = 0$. Test of $\theta_i = \theta_j$: Q(0) =	.00, $P = .\%_{0}$, $H^{2} = .$ 0.00, $p = .$	 -0.10 [-0.49, 0.29] 	Sampgann, D. 2010 24 2, 7 .251 .7 ■ 0.30 [-0.09, 0.09] Heterogenetic: * = 0.00, P = .5, H ² = . Test of θ _i = θ _i : Q(0) = 0.00, p = .
Overall Heterogeneity: x ² = 2	18 I ² = 79 30% H ² = 4.83	-0.91 [-2.83, 1.00]	Overall -0.39 [-1.70, 0.93]
Test of $\theta_i = \theta_j$: Q(2) =	6.80, p = 0.03		Heterogeneity: $\tau^2 = 0.80$, $l^2 = 58.51\%$, $H^2 = 2.41$ Test of $\theta = \theta : \Omega(2) = 4.75$, $p = 0.09$
Test of group differen	ces: Q ₆ (1) = 0.75, p = 0.39	2 0 2	Test of group differences: Q ₀ (1) = 2.21, p = 0.14
Random-effects REML Sorted by: _meta_id	. model		-6 -4 -2 0 2 Pandom-effects REML model
1	Post-interventional Serum Anio	on Gap (mmol/l)	Sorted by: _meta_d Change in Serum Anion Gap (mmol/l)
Study	Treatment Control N Mean SD N Mean SD	Mean Diff. Weig with 95% CI (%	ht Treatment Control Mean Diff. Weigh
After trial	26 126 28 20 118 21	0 80 [-0 76 - 2 26] 52 8	Study N Mean SD N Mean SD with 95% CI (%) After trial
Heterogeneity: $\tau^2 = 0$ Test of $\theta_i = \theta_j$: Q(0) =	1.00, l ² = .%, H ² = .	0.80 [-0.76, 2.36]	Djuric, P. 2020 ⁽²⁾ 26 5 2.8 2.8 4 3.1 0.10 [-1.46, 1.66] 53.27 Heterogeneity: 1* = 0.0, 1* = .*5, H* = . 0.10 [-1.46, 1.66] 53.27 0.10 [-1.46, 1.66] Test of 8, e; C(0) = -0.00, p = . 0.10 [-1.46, 1.66] 0.10 [-1.46, 1.66] 0.10 [-1.46, 1.66]
During trial Saengpanit, D. 2018	22) 24 21.5 2.7 25 18.5 4.2	3.00 [1.03, 4.97] 46.1	1 During trial (22)
Heterogeneity: $\tau^2 = 0$ Test of $\theta_i = \theta_j$: Q(0) =	1.00, I ² = .%, H ² = . 0.00, p = .	3.00 [1.03, 4.97]	Saengpanit, D. 2018 24 2.3 2.7 25 -2 4.2
Overall Heterogeneity: T ² = 1	.60, l ² = 66.07%, H ² = 2.95	1.81 [-0.33, 3.96]	
Test of $\theta_i = \theta_j$: Q(1) =	2.95, p = 0.09		Overall 1.22 [-1.13, 3.57] Heterogeneity: $\tau^2 = 2.06$, $l^2 = 71.49\%$, $H^2 = 3.51$
Test of group differen	tces: Q _b (1) = 2.95, p = 0.09	4 6	Test of $\theta_i = \theta_j$; Q(1) = 3.51, p = 0.06
Random-effects REMI Sorted by: meta id	L model		Test of group differences: Q ₆ (1) = 3.51, p = 0.06
			Random-effects REML model Sorted by: _meta_id

FIGURE 5: Meta-analysis of the effect of STS on electrolytes in patients with macrovascular calcification. Panels (**A**–**J**) show the point values (during or after the trials) and the changes from the baseline of serum sodium, potassium, chloride, bicarbonate and anion gap. During the trial period, higher anion gaps (49 participants, MD: 3.00 mmol/l, 95% CI: 1.03 to 4.97 mmol/L) and a larger increase in the anion gap (49 participants, MD: 2.50 mmol/l, 95% CI: 0.53 to 4.47 mmol/L) were noted in the STS group compared with the control group (I and J).



FIGURE 6: Analysis of the effect of STS on BMD in patients with VC. BMD in different locations was synthesized. Compared with controls, no difference was noticed in both post-interventional levels (**A**) and the change (**B**) of BMD in the STS group in both sites (lumbar and hip) (P > .05).



FIGURE 7: Risk-of-bias assessment of randomized control trials using RoB 2 tool.

DISCUSSION

To date, no medication has been approved to treat VC. Most of the conventional therapies (e.g. phosphate binders, calcimimetics, vitamin D therapy, etc.) yielded conflicting or inconclusive results [25]. Magnesium supplementation showed attenuation on VC but needs further exploration [25]. SNF472, as a new agent that directly inhibits calcium phosphate crystal formation and aggregation, has completed a Phase 2 clinical trial showing attenuation of coronary artery and aortic valve calcification in HD patients [26]. In this systematic review and

meta-analysis, we found that intravenous STS may attenuate the progression of macrovascular calcification and arterial stiffness in patients treated with HD.

In clinical trials lacking controls, a reduction or nonprogression for VC was observed among patients receiving STS. Ghiandai *et al.* [10] reported a modest reduction of Kauppila's index was detected in 18 HD patients administrated with 6-month intravenous STS. Mathews *et al.* [11] treated 22 HD patients with CAC with intravenous STS for 5 months, and no progression in the mean annualized rate of change of VC



FIGURE 8: Risk-of-bias assessment of the non-randomized control trial using ROBINS-I tool.

was observed. In our meta-analysis, comparisons were made between patients treated with and without intravenous STS, and less progression of the Agatston score for coronary artery and iliac artery in the STS group compared with controls was revealed. However, this finding was not replicated in the aorta, suggesting that diverse mechanisms might be involved (e.g. aging, smoking, metabolic disorders [27]). Progression in CVS was also compared between the two groups, but no difference was noticed. This could partly be due to the conversion from median to mean scores in meta-analysis and the fewer number of studies reporting CVS. Thus, STS's role in CVS scores may need further investigation. Compared with CVS, more evidence lies in Agatston scores for predicting CV events [28]. In addition to calcification scores, STS could help ameliorate arterial stiffness and presented prolonged benefits at 48 weeks in an extended study of Saengpanit's trial [29]. Although no benefit has been shown by current cohort studies, an overall survival improvement in patients with calciphylaxis has been reported by Gaisne et al. with an effective therapeutic regimen of STS for not <2 weeks or with a cumulative STS dose of no <150 g [30, 31]. For studies examining the effect of STS on macrovascular calcification, however, a short follow-up duration and a lack of evidence on long-term survival have been noted.

Common adverse events in prior studies on STS treatment included electrolyte disorders, GI symptoms, decreased appetite/anorexia, skin disorders, metabolic acidosis and transient hypotension/hypertension [32]. These were all noted in our review. Our study indicates that GI symptoms were the most commonly seen and might be related to fast infusion or post-dialysis administration of STS in patients treated with dialysis. Serum electrolytes and anion gap could be dramatically altered after infusion and were likely to change in the middle of a certain period of STS therapy depending on STS dosage [33]. Our analysis suggests that these effects might not last after the completion of STS therapy. However, bicarbonate supplement via dialysates or other routes might be a key element not adjusted in the included trials. Whether STS administration casts an impact on calciumphosphate metabolism has not been well-defined. For iPTH and 25(OH)VitD₃, although stated in some of the included trials, are not expected to be directly affected by STS treatment. Elevated serum calcium or phosphate levels in STS treated patients have been reported in case studies [34]. In our metaanalysis, calcium and phosphate levels seemed not impacted by STS administration both during and after the completion. BMD seemed not to be impacted by STS use in our analysis, but a paucity of evidence should be noted. To avoid unnecessary risks and make the best use of the therapy, close observation and dynamic regimen adjustment are suggested.

Several limitations should be noted in the present study. First, the trials included in our analysis only provided perprotocol data in which the effect size may be exaggerated. Second, some of the subgroups (e.g. Agatston scores, BMD) were derived from duplicated participants. Here, we should concentrate on the subgroup effects and the between-group differences rather than the overall effects. Third, missing data, various sources of heterogeneity and a high risk of bias are notable. We reached out to the primary study authors via email to address the missing data. No reply, however, was obtained. Of note, the sample size was relatively small in current studies included given the paucity of randomized trials in this area. Furthermore, the absence of calcimimetics or non-calcium-based phosphate binder's use may make the participants included less representative of patients with easy access to those medications. Nonetheless, this meta-analysis is the first to systematically examine and report the current state of knowledge on the effects of STS for VC in CKD patients.

In conclusion, intravenous STS may attenuate the progression of VC and arterial stiffness in individuals on HD. Future large and well-designed randomized controlled trials are warranted to further establish the effect of STS.

SUPPLEMENTARY DATA

Supplementary data are available at *ndt* online.

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AUTHORS' CONTRIBUTIONS

S.U.N. and W.W. conceived the study. W.W. and I.P.-C. were involved in data collection, statistical design and analysis. W.W., R.S., D.K., S.K., J.G., R.M.N., V.C., R.M., R.K., C.K.M. and S.U.N. were involved in the study design, analysis and editing of the manuscript. All authors contributed to the article and approved the submitted version.

CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data used or analyzed in the study are available from the corresponding author on reasonable request.

REFERENCES

- Sin HK, Wong PN, Lo KY *et al.* An echocardiography-derived calcium score as a predictor of major adverse cardiovascular events in peritoneal dialysis patients--a prospective cohort study. *Nephrology (Carlton)* 2022; 27: 181–189
- 2. Chen L, Vavrenyuk A, Ren JH *et al.* Prognostic value of coronary artery calcification identified by the semi-quantitative weston method in the emergency room or other hospitalized patients. *Front Cardiovasc Med* 2021; 8: 684292
- Dusing P, Zietzer A, Goody PR et al. Vascular pathologies in chronic kidney disease: pathophysiological mechanisms and novel therapeutic approaches. J Mol Med (Berl) 2021; 99: 335–348
- Kakani E, Elyamny M, Ayach T, El-Husseini A. Pathogenesis and management of vascular calcification in CKD and dialysis patients. *Semin Dial* 2019; 32: 553–561

- Nelson AJ, Raggi P, Wolf M et al. Targeting vascular calcification in chronic kidney disease. JACC Basic Transl Sci 2020; 5: 398–412
- Chen HC, Wang WT, Hsi CN *et al.* Abdominal aortic calcification score can predict future coronary artery disease in hemodialysis patients: a 5year prospective cohort study. *BMC Nephrol* 2018; 19: 313
- Piccoli GB, Torreggiani M, Gendrot L *et al.* Setting the clock back: new hope for dialysis patients. Sodium thiosulphate and the regression of vascular calcifications. *J Nephrol* 2021; 34: 23–25
- Cicone JS, Petronis JB, Embert CD *et al.* Successful treatment of calciphylaxis with intravenous sodium thiosulfate. *Am J Kidney Dis* 2004; 43: 1104–1108
- 9. Pasch A, Schaffner T, Huynh-Do U *et al.* Sodium thiosulfate prevents vascular calcifications in uremic rats. *Kidney Int* 2008; 74: 1444–1453
- Ghiandai G, Ralli C, Imperiali P *et al.* [Is the Sodium Thiosulfate Therapy useful for vascular calcification in dialysis Pts?]. *G Ital Nefrol* 2015; 32: gin/32.3.6
- 11. Mathews SJ, De Las Fuentes L, Podaralla P *et al.* Effects of sodium thiosulfate on vascular calcification in end-stage renal disease: a pilot study of feasibility, safety and efficacy. *Am J Nephrol* 2011; 33: 131–138
- Chen NC, Hsu CY, Chen CL. The strategy to prevent and regress the vascular calcification in dialysis patients. *Biomed Res Int* 2017; 2017: 9035193
- Selk N, Rodby RA. Unexpectedly severe metabolic acidosis associated with sodium thiosulfate therapy in a patient with calcific uremic arteriolopathy. *Semin Dial* 2011; 24: 85–88
- Dobry AS, Ko LN, Kroshinsky D. Fractures in calciphylaxis patients following intravenous sodium thiosulfate therapy. J Eur Acad Dermatol Venereol 2017; 31: e445–e446
- Levey AS, Eckardt KU, Dorman NM *et al.* Nomenclature for kidney function and disease-executive summary and glossary from a Kidney Disease: Improving Global Outcomes (KDIGO) consensus conference. *Eur Heart J* 2020; 41: 4592–4598
- Yang ZR, Sun F, Zhan SY. [Risk on bias assessment: (2) revised cochrane risk of bias tool for individually randomized, parallel group trials (RoB2.0)]. *Zhonghua Liu Xing Bing Xue Za Zhi* 2017; 38: 1285–1291
- Sterne JA, Hernan MA, Reeves BC *et al.* ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ* 2016; 355: i4919
- Wan X, Wang W, Liu J *et al.* Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol* 2014; 14: 135
- Adirekkiat S, Sumethkul V, Ingsathit A *et al.* Sodium thiosulfate delays the progression of coronary artery calcification in haemodialysis patients. *Nephrol Dial Transplant* 2010; 25: 1923–1929
- Messa M, Tomei P, Motton M *et al.* Effect of sodium thiosulphate on aortic calcifications in hemodialysis patients. *Nephrol Dial Transplant* 2014; 29: iii48
- Yu Y, Bi ZM, Wang Y *et al.* [Effect of sodium thiosulfate on coronary artery calcification in maintenance hemodialysis patients]. *Zhonghua Yi Xue Za Zhi* 2016; 96: 3724–3728
- 22. Saengpanit D, Chattranukulchai P, Tumkosit M *et al.* Effect of sodium thiosulfate on arterial stiffness in end-stage renal disease patients undergoing chronic hemodialysis (Sodium Thiosulfate-Hemodialysis study): a randomized controlled trial. *Nephron* 2018; 139: 219–227
- Djuric P, Dimkovic N, Schlieper G et al. Sodium thiosulphate and progression of vascular calcification in end-stage renal disease patients: a double-blind, randomized, placebo-controlled study. Nephrol Dial Transplant 2020; 35: 162–169
- Bian Z, Zhang Q, Shen L *et al.* The effect of sodium thiosulfate on coronary artery calcification in hemodialysis patients. *ASAIO J* 2022; 68: 402–406
- Xu C, Smith ER, Tiong MK *et al.* Interventions to attenuate vascular calcification progression in chronic kidney disease: a systematic review of clinical trials. *J Am Soc Nephrol* 2022; 33: 1011–1032
- Raggi P, Bellasi A, Bushinsky D *et al.* Slowing progression of cardiovascular calcification with SNF472 in patients on hemodialysis: results of a randomized phase 2b study. *Circulation* 2020; 141: 728–739
- 27. Singh A, Tandon S, Tandon C. An update on vascular calcification and potential therapeutics. *Mol Biol Rep* 2021; 48: 887–896

- Blaha MJ, Mortensen MB, Kianoush S et al. Coronary artery calcium scoring: is it time for a change in methodology? JACC Cardiovasc Imaging 2017; 10: 923–937
- 29. Saengpanit D, Sitprija V, Praditpornsilpa K *et al.* Effect of sodium thiosulfate on arterial stiffness in end-stage renal disease patients undergoing chronic hemodialysis: an extended follow-up of the sodium thiosulfate-hemodialysis study (a randomized controlled trial). *Nephrol Dial Transplant* 2019; 34: a254
- Udomkarnjananun S, Kongnatthasate K, Praditpornsilpa K et al. Treatment of calciphylaxis in CKD: a systematic review and meta-analysis. *Kidney Int Rep* 2019; 4: 231–244
- 31. Gaisne R, Péré M, Menoyo V et al. Calciphylaxis epidemiology, risk factors, treatment and survival among French chronic

kidney disease patients: a case-control study. BMC Nephrol 2020; 21:63

- 32. Nigwekar SU, Brunelli SM, Meade D *et al.* Sodium thiosulfate therapy for calcific uremic arteriolopathy. *Clin J Am Soc Nephrol* 2013; 8: 1162–1170
- Hundemer GL, Fenves AZ, Phillips KM *et al.* Sodium thiosulfate and the anion gap in patients treated by hemodialysis. *Am J Kidney Dis* 2016; 68: 499–500
- 34. Hlusicka J, Veisova E, Ullrych M *et al.* Serum calcium and phosphorus concentrations and the outcome of calciphylaxis treatment with sodium thiosulfate. *Monatshefte für Chemie Chem Mon* 2017; 148: 435–440

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