

Supplemental Material

Data S1. Search Strategy.

Ovid MEDLINE(R) <1946 to November 7, 2022> and Embase Classic + Embase <1947 to November 7, 2022)

1. vascular calcification or arter* calcification or aortic calcification or coronary calcification or coronary artery calci* or valv* calcification or CAC.mp
2. exp vascular calcification/
3. 1 or 2
4. Limit 3 to (clinical trial or randomised controlled trial or controlled clinical trial)
5. (random* control* trial* or clinical trial* or control* clinical trial* or rct).mp
6. 3 and 5
7. 4 or 6
8. Remove duplicates from 7

Ovid MEDLINE(R) <1946 to October 8, 2023> and Embase Classic + Embase <1947 to October 8, 2023)

1. dense calci* or calci* plaque
2. limit 1 to (clinical trial or randomised controlled trial or controlled clinical trial)

Table S1. Risk of bias assessment for included RCTs.

Author and Year	Random sequence generation	Allocation concealment	Blinding		Incomplete outcome data assessed (attrition)	Lack of selective outcome reporting	Lack of other sources of bias	Overall evaluation
			Participants, investigators (performance)	Outcome assessors (detection)				
Arad 2005 ¹¹	Yes	Not described	Yes	Yes	Intention to treat analysis (with 18.4% total dropout)	Yes	Yes, but industry provided study medication	Moderate RoB due to attrition bias
Cowell 2005 ¹²	Yes	Yes	Yes	Yes	Uneven loss of follow up (9% treatment, 5% placebo)	Yes	Yes, but industry provided study medication	Moderate RoB due to attrition bias
Dichtl 2008 ¹³	Yes	Not described	Not described	Not described	Even loss of follow up	Yes	Yes, but industry provided study medication	High RoB in the absence of reporting across domains
Egede 2013 ⁵⁰	Yes	Not described	Yes	Yes	Even loss of follow up	Yes	Yes	Low RoB
Hougaard 2020 ⁵³	Yes	Not described	Yes	Yes	Even loss of follow up	Yes	Yes	Low RoB
Lee 2016 ⁵²	Yes	Not described	No	No	Probably no loss of follow up	Yes	Probably no – industry provided funding	High RoB due to performance and detection bias
Lo 2015 ⁵¹	Yes	Not described	Yes	Yes	Uneven loss of follow up (11% treatment, 5% placebo)	Yes	Probably no – industry provided funding	High RoB due to attrition and industry involvement
Houslay 2006 ¹⁴	Yes	Yes	Yes	Yes	Uneven loss of follow up (18% treatment, 15% placebo)	Yes	Yes, but industry provided study medication	Low RoB

Longenecker 2016¹⁵	Yes	Not reported	Yes	Yes	Uneven loss of follow up (7% treatment, 13% placebo)	Yes	Probably no – industry provided study medication and sponsor	High RoB due to attrition and industry involvement
Miyoshi 2018¹⁶	Yes	Not reported	Not reported	Yes	Uneven loss of follow up (5% vs 10% vs 6%)	Yes	Yes	Moderate RoB due to lack of reporting across domains
Park 2016⁴⁹	Yes	Not reported	Yes	Yes	Not described (28% total dropout)	Yes	Yes	Moderate RoB due to probable attrition bias
Petri 2011¹⁷	Yes	Not reported	Yes	Yes	Uneven loss of follow up (1% treatment, 4.5% placebo)	Yes	Yes, but industry sponsored	Low RoB
Plazak 2011¹⁸	Yes	Not reported	Yes	Yes	Probably no loss of follow up	Yes	Yes	Low RoB
Raggi 2005¹⁹	Yes	Probably yes	Yes	Yes	Intention-to-treat analysis with uneven loss of follow up (14% treatment vs 8% control)	Yes	Probably no – industry provided study medication and sponsor	Moderate RoB (industry involvement and attrition)
Schmermund 2006²⁰	Yes	Probably yes	Yes	Yes	Uneven loss to follow up (20% treatment, 14% comparator)	Yes	Yes, but industry sponsor	Moderate RoB (industry involvement and attrition)
Terry 2007²¹	Yes	Yes	Yes	Yes	Even loss of follow up	Yes	Yes, but industry sponsor	Low RoB
Budoff 2009²²	Yes	Probably yes	Yes	Yes	Even loss of follow up	Yes	Probably no - industry provided	Moderate RoB due to industry involvement

							study medication and sponsor	
Budoff 2004²³	Yes	Yes	Yes	Yes	Even loss of follow up	Yes	Probably no – industry provided study medication and sponsor	Low RoB
Matsumoto 2014²⁴	Probably yes	Not reported	Yes	Yes	Even loss of follow up	Yes	Yes, but some industry sponsorship and provision of study medication	Moderate RoB due to industry involvement and lack of comprehensive description across domains
Shaikh 2020²⁵	Yes	Not reported	Yes	Yes	Not described (17.5% total dropout)	Yes	Yes	Moderate RoB due to absence of reporting across domains
Wlosinska 2020²⁷	Yes	Yes	Yes	Yes	Even loss of follow up	Yes	Probably no – industry provided study medication and sponsor	Low RoB
Zeb 2012²⁶	Yes	Yes	Yes	Yes	Uneven loss of follow up (27% treatment, 19% placebo)	Yes	Probably no – industry provided study medication and sponsor	Moderate RoB due to attrition and industry involvement
Basaria 2015²⁸	Yes	Yes	Yes	Yes	Even loss of follow up	Yes	Probably no – industry sponsored	Low RoB
Budoff 2017²⁹	Probably yes	Probably yes	Yes	Yes	Even loss of follow up	Yes	Probably no – industry involvement	Moderate RoB
Harman 2014³⁰	Yes	No	Yes	Yes	Even loss of follow up	Yes	Probably no	Low RoB

Bellinge 2021³¹	Yes	Yes	Yes	Yes	Uneven loss of follow up (5% vs 5% vs 3% vs 0%)	Yes	Yes	Low RoB
Brandenburg 2017³²	Probably yes	Not reported	Not reported	Yes	Uneven loss of follow up (32% treatment, 44% placebo)	Yes	Probably no – industry sponsored	High RoB due to attrition and absence of reporting across domains
Diederichsen 2022⁵⁴	Yes	Yes	Yes	Yes	Uneven loss of follow up (6% treatment vs 11% placebo)	Yes	Probably yes	Moderate RoB
Shea 2009³³	Yes	Not reported	Yes	Yes	Even loss of follow up	Yes	Probably yes	Low RoB
Zwakenberg 2019³⁴	Yes	Not reported	Yes	Yes	Uneven loss of follow up (6% treatment, 18% placebo)	Yes	Probably yes	Moderate RoB due to attrition
Henzel 2021⁵⁸	Yes	Not reported	No	Yes	Even loss of follow up	Yes	Probably yes	Moderate RoB due to performance bias
Fitch 2012⁵⁹	Yes	Yes	No in the lifestyle arm	Yes	Uneven loss of follow up	Yes	Probably yes	Moderate RoB due to attrition and performance bias
Kuller 2011³⁵	Yes	No	No	Probably no	Uneven loss of follow up (13% treatment, 8% control)	Yes	Probably yes	High RoB due to performance, detection and attrition bias
Lehmann 2011³⁶	Yes	Not reported	No	Yes	Even loss of follow up	Yes	Yes	Moderate RoB due to performance bias
Lee 2017³⁷	Yes	Not reported	Not reported	Yes	Uneven loss of follow up (5%	Yes	Yes	Moderate RoB due to insufficient

					treatment, 10% control)			reporting across domains, and attrition
Lee 2019³⁸	Yes	Not reported	No	Yes	Uneven loss of follow up (10% treatment, 6% control)	Yes	Yes	Moderate RoB due to performance and attrition bias
Lee 2018³⁹	Yes	Probably no	No	No	Uneven loss of follow up (7% treatment, 15% control)	Yes	Probably yes	Moderate RoB due to performance and attrition bias
Win 2019⁴⁰	Yes	Not reported	No	Yes	Uneven loss of follow up (21% treatment, 9% control)	Yes	Yes but industry sponsor	High RoB due to performance and attrition bias, and industry involvement
Kranenburg 2018⁴¹	Yes	Not reported	Yes	Yes	Even loss of follow up	Yes	Probably yes	Low RoB
Pawade 2021⁴²	Yes	Yes	Yes	Yes	Uneven loss of follow up (14% treatment 1, 10% treatment 2, 8% placebo)	Yes	Probably yes	Moderate RoB due to attrition
Motro 2000⁴³	Yes	Not reported	Yes	Yes	Even loss of follow up (intention to treat)	Yes	Yes but industry sponsor	Low RoB
Motro 2007⁴⁴	Yes	Not reported	Yes	Yes	Even loss of follow up	Yes	Yes, but industry sponsor	Low RoB
Alfaddagh 2017⁵⁶	Yes	Probably yes	No	Yes	Uneven loss of follow up (15% treatment vs 32%	Yes	Probably yes	Moderate RoB due to attrition bias

					placebo); intention-to- treat			
Budoff 2020⁵⁵	Yes	Not reported	Yes	Yes	Uneven loss of follow (23% treatment vs 7.5% placebo); intention-to- treat	Yes	Probably no – industry involvement and sponsor	High RoB due to attrition bias and industry involvement
Davidson 2010⁴⁵	Yes	Not reported	Yes	Yes	Even loss of follow up	Yes	Probably no – industry involvement and sponsor	Moderate RoB due to industry involvement
Hauser 2016⁴⁶	Yes	Probably yes	Yes	Yes	Uneven loss of follow up (35% treatment, 30% placebo)	Yes	Probably no- industry sponsor and provided study drug	Moderate RoB due to industry involvement and attrition bias
Hodis 2009⁴⁷	Yes	Yes	Yes	Yes	Even loss of follow up (intention to treat)	Yes	Yes, but industry sponsor	Low RoB
Joshi 2016⁴⁸	Yes	Not reported	Yes	Yes	Not reported	Yes	Probably yes	Moderate RoB due to absence of reporting across domains
Nozue 2016⁵⁷	Yes	Not reported	No	No	Uneven loss of follow up (0% treatment vs 15% placebo)	Yes	Probably yes	High RoB due to performance, detection and. Attrition bias

Table S2. Summary of GRADE findings.

Intervention	Risk of bias	Consistency	Imprecision	Indirectness	Publication bias (no. of studies)	Quality of evidence (GRADE)
Lipid-lowering agents	Moderate	All RCTs, consistent results	None	Non-CKD population	16	⊕⊕⊕○ Due to risk of bias
Aged garlic extract	Moderate	All RCTs, consistent results	Few participants	Non-CKD population	6	⊕⊕○○ Due to risk of bias and imprecision
Hormone replacement therapy	Low	All RCTs, consistent results	None	Non-CKD population	3	⊕⊕⊕⊕ Minimal bias, imprecision
Vitamin K	Moderate	All RCTs, inconsistent results	None	Non-CKD population	5	⊕⊕⊕○ Due to risk of bias
Lifestyle	Moderate	All RCTs, inconsistent results	None	Non-CKD population	4	⊕⊕○○ Due to risk of bias and publication bias
Anti-thrombosis / anti-coagulant therapy	Moderate	All RCTs, consistent results	Few participants	Non-CKD population	4	⊕⊕○○ Due to risk of bias and publication bias
Antiresorptive	Low	All RCTs, inconsistent results	Few participants	Non-CKD population	2	⊕○○○ Due to risk of bias,

						imprecision and publication bias
Antihypertensive	Low	All RCTs, inconsistent results	None	Non-CKD population	2	⊕⊕⊕⊕ Due to publication bias
Hypoglycaemic agents	Moderate	All RCTs, inconsistent results	Few participants	Non-CKD population	2	⊕○○○ Due to risk of bias, imprecision and publication bias
Omega-3 fatty acids	Moderate	All RCTs, consistent results	Few participants	Non-CKD population	2	⊕○○○ Due to risk of bias, imprecision and publication bias
Salsalate	Moderate	Single RCT	Few participants	Non-CKD population	1	⊕○○○ Due to risk of bias, imprecision and publication bias
Folic acid	Low	Single RCT	None	Non-CKD population	1	⊕⊕○○ Due to imprecision and publication bias
Dalcetrapib	Moderate	Single RCT	Few participants	Non-CKD population	1	⊕○○○ Due to risk of bias, imprecision and publication bias