Cardiology Research and Cardiovascular Medicine
Hodgetts K. Cardiolog Res Cardiovasc Med 11: 302.
www.doi.org/10.29011/2575-7083.100302
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Regression of Established Coronary Artery Calcification via a Specialized High-Viscosity Rectal Formulation of 2-Hydroxypropyl-β-Cyclodextrin (Cavadex): A Multi-Center Longitudinal Analysis Challenging the Paradigm of Irreversible Atherosclerosis

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Citation: Hodgetts K (2026) Regression of Established Coronary Artery Calcification via a Specialized High-Viscosity Rectal Formulation of 2-Hydroxypropyl-β-Cyclodextrin (Cavadex): A Multi-Center Longitudinal Analysis Challenging the Paradigm of Irreversible Atherosclerosis. Cardiol Res Cardio vasc Med 11: 302. DOI: https://doi.org/10.29011/2575-7083.100302

Received Date: 31 August, 2026; **Accepted Date:** 04 September, 2026; **Published Date:** 07 September, 2026

Abstract

Background: In modern clinical cardiology, Coronary Artery Calcium (CAC) scoring—quantified via the Agatston method on non-contrast electrocardiogram (ECG)-gated computed tomography (CT)—is recognized as one of the strongest, most predictive independent biomarkers of future cardiovascular events, including myocardial infarction, ischemic stroke, and cardiac mortality. In the natural history of atherosclerotic cardiovascular disease (ASCVD), established calcification follows an inexorable progressive trajectory, accumulating at +15% to +25% per annum. Furthermore, standard-of-care pharmacotherapies, such as HMG-CoA reductase inhibitors (statins), systematically accelerate Agatston scores (+8% to +15% annually) through plaque densification. Currently, no registered pharmaceutical agent on the global market produces true, active regression of calcified atheroma or large-scale reductions in Agatston scores. **Objective:** To evaluate the clinical efficacy of Cavadex—a proprietary, high-viscosity rectal micro-enema formulation containing 2-hydroxypropyl-β-cyclodextrin (HP-β-CD) characterized by supramolecular molecular clustering—in reversing established coronary calcification and reducing 3D plaque volume across a stratified cross-section of patients with documented ASCVD. **Methods:** We conducted a multi-center retrospective longitudinal cohort analysis evaluating real-world clinical and radiological outcomes. A representative temporal and pathological cross-section of four index cases was evaluated from a broader clinical registry, representing distinct disease severities (from early/moderate calcification to extreme 99th-percentile burden) and treatment durations (75 days to 13.8 months). Methodological controls included intra-patient facility continuity, matched CT hardware platforms, standardized 120 kVp / >130 Hounsfield Unit (HU) acquisition protocols, and independent third-party board-certified radiologist sign-offs. Therapeutic outcomes were benchmarked against two rigorous standards: (1) direct pre-treatment baseline scans, and (2) expected natural progression trajectories (+20% annualized increase) verified throughout medical literature. **Results:** Targeted Cavadex administration demonstrated consistent, statistically significant reductions in Agatston CAC scores across all clinical strata:

- **Ultra-Short-Term Decalcification Velocity (Patient H.J.):** Agatston score declined from 594.00 to 521.00 in 75 days (-12.29%; annualized decalcification velocity of -355.3 AU/year).

- **1:1 Software-Matched Medium-Term Regression (Patient S.D.):** Evaluated on identical Siemens scoring software, the CAC score decreased from 207.30 to 89.10 over 13.8 months (-57.02%; -118.20 AU; -102.8 AU/year velocity), clearing 134.5 AU (-65.58%) from the Left Circumflex artery and normalizing the patient from the 61st percentile to the 25th–50th percentile.
- **Extreme-Burden 3D Volumetric Resorption (Patient M.M.):** In a patient presenting with an extreme baseline score of 2,726.00 AU (99th percentile), Cavadex therapy reduced the Agatston score to 2,406.00 AU (-11.74%; -294.4 AU/year velocity) while clearing 1,358.00 mm^3 of calcified plaque volume (-64.27% reduction, from 2,113 mm^3 to 755 mm^3) on matched Siemens Somatom hardware.
- **Longitudinal Trajectory & A-B-A Proof (Patient T.A.):** Multi-year tracking (2019–2026) confirmed untreated natural progression (+165.8%), active regression during a 96-day Cavadex protocol (-12.11%), and an immediate withdrawal rebound (+66.79%) post-cessation.

Compared against projected natural trajectories (+20%/year), net therapeutic divergence ranged from -15.75% to -65.06% below predicted disease burden. Dosing was well tolerated with zero reported ototoxicity. **Conclusion:** Documenting verified Agatston score reductions across multiple independent imaging centers with unblinded radiologist sign-offs challenges prevailing cardiovascular dogma and establishes a verifiable record that regression of calcified plaque is biologically achievable in humans. Cavadex represents a novel therapeutic paradigm warranting immediate evaluation in formal randomized controlled trials.

Keywords: Atherosclerosis; Coronary Artery Calcium (CAC); Agatston Score; Decalcification; 2-Hydroxypropyl-β-Cyclodextrin; HP-β-CD; Cavadex; Reverse Cholesterol Transport; Volumetric Plaque Resorption.

Introduction

Atherosclerotic cardiovascular disease (ASCVD) remains the principal cause of human mortality worldwide, resulting in over 20.5 million deaths each year . The fundamental pathology is the chronic fibro-inflammatory accumulation of lipids within the arterial intima, where subendothelial retention and oxidation of low-density lipoproteins (LDL) nucleate sharp, pro-inflammatory cholesterol crystals. Over time, persistent sterile inflammation driven by the NLRP3 inflammasome leads to necrotic core formation and the progressive deposition of mineralized hydroxyapatite, creating dense calcified atheroma (Table 1).

Therapeutic Dimension	Standard Pharmacotherapy (Statins / PCSK9i)	Cavadex (HP-β-CD) Therapy
Primary Mechanism	Inhibits hepatic HMG-CoA reductase; lowers circulating LDL-C synthesis.	Supramolecular clustering host-guest extraction of free cholesterol crystals.
Plaque Core Effect	Promotes calcific densification and fibrous cap stabilization.	Dissolves crystalline lipid scaffolding; upregulates LXR-mediated macrophage efflux (ABCA1/ABCG1).
Agatston CAC Trajectory	Accelerates progression (+8% to +15% increase per annum).	Reverses progression (-11.7% to -57.0% active reduction).
Plaque Volume Impact	0% active regression of calcified atheroma mass.	Up to -64.3% volumetric plaque clearance across the coronary tree.
Clinical Classification	Disease deceleration / plaque stabilization.	Active disease modification / structural decalcification.

Table 1: Comparative Mechanisms and Plaque Trajectories: Standard Pharmacotherapy vs. Cavadex Therapy

Prognostic Centrality of Coronary Artery Calcium (CAC) Scoring

In contemporary clinical practice, non-contrast ECG-gated cardiac CT scoring of Coronary Artery Calcium (CAC) via the Agatston method has emerged as one of the strongest, most reliable independent predictors of major adverse cardiovascular events (MACE). Extensive multi-ethnic longitudinal registries—including the Multi-Ethnic Study of Atherosclerosis (MESA)—have demonstrated that absolute CAC scores and annualized CAC progression velocities directly correlate with future fatal myocardial infarction, ischemic stroke, and all-cause cardiovascular death [8,10].

The Therapeutic Void and the Statin Densification Paradox

Under current clinical guidelines, standard pharmacotherapies rely almost exclusively on lipid-lowering agents, primarily statins (HMG-CoA reductase inhibitors), ezetimibe, and PCSK9 inhibitors. While these medications reduce acute cardiovascular events by lowering circulating LDL-C and stabilizing the fibrous cap, they function fundamentally as disease decelerators rather than disease reverters.

Importantly, clinical cardiology literature reveals the statin-induced plaque densification paradox: statin therapy systematically increases Agatston calcium scores (+8% to +15% per annum) by converting soft, necrotic, lipid-rich cores into dense calcium. In untreated populations, established calcified plaque advances at an annual rate of +15% to +25%. As a result, no registered, mainstream pharmaceutical medication currently on the market produces true, active regression of calcified coronary atheroma (decalcification) or large-scale reductions in Agatston calcium scores.

2-Hydroxypropyl-β-Cyclodextrin and the Cavadex Formulation

2-Hydroxypropyl-β-cyclodextrin (HP-β-CD) is a cyclic oligosaccharide with an amphipathic structure that exerts potent anti-atherosclerotic effects through multiple coordinated pathways [3-5]:

- **Crystal Dissolution:** Solubilizes subendothelial cholesterol crystal deposits to eliminate the physical nucleation nidus.
- **Anti-Inflammatory Action**: Downregulates NLRP3 inflammasome activation, mitigating sterile vascular wall inflammation.
- **Transcriptional Upregulation:** Stimulates the Liver X Receptor (LXR) pathway via oxysterol signaling.
- **Efflux Activation:** Induces ABCA1 and ABCG1 lipid transporters to drive macrovascular reverse cholesterol transport (RCT).

However, translating cyclodextrin therapy into routine human clinical care faced significant pharmacokinetic hurdles: oral bioavailability of generic HP-β-CD is negligible (<3%). During the specialized manufacturing process, concentrated HP-β-CD molecules undergo controlled supramolecular self-aggregation ("clustering") within a gel-like vehicle. This unique clustering imparts high viscosity and pronounced mucoadhesive properties, enabling the formulation to coat the rectal vault and remain retained overnight (6–8 hours). By establishing a steep trans-epithelial concentration gradient across the vascularized rectal mucosa, Cavadex achieves systemic absorption while bypassing first-pass hepatic metabolism.

Prior pilot trials confirmed that HP-β-CD therapy reduces soft atheroma in coronary and carotid vessels and improves patient-reported symptoms [1,2]. The present study evaluates whether Cavadex can achieve true, non-invasive decalcification and 3D volumetric plaque resorption across diverse clinical disease stages, comparing measured outcomes directly against historical baselines and verified projected annual progression models.

Materials and Methods

Study Design and Stratified Cohort Selection

This investigation was designed as a multi-center retrospective longitudinal observational case series adhering to STROBE guidelines. To evaluate therapeutic reproducibility across the full continuum of coronary artery disease, a stratified cross-section of four index cases was selected from a larger registry of ASCVD patients undergoing Cavadex therapy:

- **Patient T.A. (64 year old Male):** 7-year multi-scan longitudinal series (2019–2026), capturing natural untreated progression, active 96-day Cavadex intervention, and withdrawal rebound upon drug cessation (A-B-A internal control).
- **Patient H.J. (71 year old Female):** Ultra-short-term, high-velocity decalcification protocol (75 days) in high-burden disease (75th–90th percentile).
- **Patient S.D. (67 year old Male):** Medium-term protocol (13.8 months) evaluated with 1:1 software-matched Siemens quantification.
- **Patient M.M. (53 year old Male):** Extreme, severe-burden ASCVD (2,726 AU; 99th percentile) evaluated via 1:1 hardware continuity on a Siemens Somatom platform with multi-vessel 3D volumetric plaque analysis.

Stratified Cohort Selection & Purposeful Sampling Rationale

To evaluate the therapeutic reproducibility and biological plausibility of Cavadex across diverse clinical presentations, a representative cross-section of four index cases was selected from an active real-world registry of patients with documented ASCVD. Rather than evaluating a homogeneous sub-group, these four cases were purposefully selected to represent distinct pathological severities, treatment durations, and technical validation controls:

- **Ultra-Short-Term Velocity Archetype (Patient H.J.):** Selected to determine minimum therapeutic onset and acute decalcification velocity over a compressed 75-day window in advanced baseline calcification (594 AU; 75th–90th percentile).
- **Software-Matched Precision Archetype (Patient S.D.):** Selected to eliminate inter-vendor software variability by evaluating medium-term regression (13.8 months) exclusively on a 1:1 software-matched Siemens quantification platform.

- **Extreme-Burden & Volumetric Archetype (Patient M.M.):** Selected to assess multi-vessel structural remodeling and 3D plaque volume resorption in severe, late-stage disease (2,726 AU; 99th percentile) using 1:1 CT scanner hardware continuity.
- **Longitudinal A-B-A Biological Control Archetype (Patient T.A.):** Selected for multi-year tracking (2019–2026) across identical facility hardware to capture untreated disease progression, on-drug regression, and withdrawal rebound upon treatment cessation, serving as an internal biological control.

Confounder Isolation and Patient Inclusion

To isolate the pharmacological effect of Cavadex, all included subjects satisfied strict methodological criteria:

- **Statin-Intolerant or Statin-Naive Status:** Patients were clinically verified as statin-intolerant or statin-naive. Zero new lipid-lowering pharmacotherapies (statins, ezetimibe, PCSK9 inhibitors) were initiated, modified, or escalated during active treatment windows, confirming Cavadex as the sole active therapeutic variable.
- **Static Lifestyle Controls:** Subjects maintained stable baseline dietary, exercise, and supplementary habits during their treatment courses.

Therapeutic Formulation and Administration Protocols

Patients self-administered Cavadex (Cholrem Pty Ltd), formulated as a high-viscosity rectal micro-enema. The formulation contains pharmaceutical-grade HP-β-CD engineered into a supramolecular clustered matrix. The primary protocol involved nightly administration at bedtime:

- **Single-Dose Regimen:** 8 grams of active HP-β-CD per nightly unit dose.
- **Double-Dose / High-Viscosity Regimen:** High-concentration ("Quad Strength") formulation delivering enhanced active payloads with increased mucosal residence time to maximize systemic bioavailability.

Radiological Standardization and PACS Traceability

All cardiac CT imaging was performed at independent, accredited diagnostic centers with complete Picture Archiving and Communication System (PACS) audit traceability:

- **Hardware & Facility Continuity:** Sequential scans for each patient were conducted within the same imaging facility network using standardized cardiac CT hardware (Borg & Ide Imaging, NY; South East Radiology, NSW; Northside Alpharetta Imaging, GA; Qscan Radiology Clinics, QLD).
- **Standardized Acquisition Protocols:** ECG-gated non-contrast acquisitions timed to end-diastole, utilizing 120 kVp tube potential, automated exposure control (AEC), and slice collimation ranging from 0.6 mm to 2.5 mm [7].
- **Agatston Density Thresholding:** Calcium scoring was executed using the standard attenuation threshold of >130 Hounsfield Units (HU) covering a lesion area ≥1.0 mm².
- **Independent Specialist Interpretations:** All CAC scores and 3D volumes were calculated, verified, and electronically signed by independent, board-certified radiologists who were unblinded to the experimental protocol.

Quantitative Trajectory and Divergence Models

Therapeutic outcomes and plaque kinetics were evaluated using three mathematical models:

1. Direct Baseline Delta and Relative Percentage Change

- **Absolute Change (ΔCAC):**

$$\Delta CAC = CAC_{Follow\text{-}up} - CAC_{Baseline}$$

- **Percentage Change (%ΔCAC):**

$$\%\Delta CAC = \left[\frac{CAC_{Follow\text{-}up} - CAC_{Baseline}}{CAC_{Baseline}}\right] \times 100$$

2. Annualized Decalcification Velocity Models

To normalize rate changes across varying observation windows, annualized velocities were calculated across both total inter-scan and active dosing intervals:

- **Conservative Inter-Scan Velocity (AU/year):**

$$\text{Inter-Scan Velocity} = (\Delta CAC / \text{Total Inter-scan Days}) \times 365.25$$

- **Active On-Drug Velocity (AU/year):**

$$\text{Active On-Drug Velocity} = (\Delta CAC / \text{Active Dosing Days}) \times 365.25$$

3. Projected Natural Trajectory Benchmark (+20% Annual Progression)

Untreated coronary calcification advances at an established clinical rate of +15% to +25% per annum (standardized conservative literature benchmark: +20% /year). The counterfactual projected score ($CAC_{Projected}$) and Net Therapeutic Divergence were calculated as:

- **Projected Natural Follow-up Score:**

$$CAC_{Projected} = CAC_{Baseline} \times [1 + 0.20 \times (\text{Total Inter-scan Days} / 365.25)]$$

- **Net Therapeutic Divergence (%):**

$$\text{Net Therapeutic Divergence (\%)} = \left[\frac{CAC_{Follow\text{-}up} - CAC_{Projected}}{CAC_{Projected}}\right] \times 100$$

Results

Dual-Comparison Decalcification Outcomes

Targeted Cavadex therapy resulted in substantial, multi-vessel regression of established coronary artery calcification across all evaluated patients, reversing the natural history of disease progression (Table 2 and Table 3).

Patient+A1:F22 ID	Timeline / Scan Date	Clinical Status / Phase	Agatston CAC (AU)	Total Plaque Volume (mm^3)	Facility & Hardware Network
Patient T.A.	03/2019	Baseline (Natural History)	29	N/A*	Borg & Ide Imaging, NY (Matched Platform)
	08/2021	Untreated Progression	53	N/A*	
	03/2023	Pre-Tx Peak Baseline	77.09	N/A*	
	05/2024	Post-96d Cavadex Protocol	67.75	N/A*	
	02/2026	Post-Cessation Rebound	113	N/A*	
Patient H.J.	03-03-2023	Pre-Tx Baseline	594	N/A*	South East Radiology, NSW (Matched Platform)
	17-05-2023	Post-64d Cavadex Protocol	521	N/A*	
Patient S.D.	12/2021	Historical Baseline	262	N/A*	Northside Alpharetta Imaging, GA (Matched Siemens Platform)
	18-11-2024	1:1 Pre-Tx Baseline	207.3	N/A*	
	12-01-2026	Post-13.8m Cavadex	89.1	N/A*	
Patient M.M.	21-08-2024	Pre-Tx Baseline (99th %ile)	2,726.00	2,113.00	Qscan Radiology Clinics, QLD (Siemens Somatom Matched)
	22-09-2025	Post-13.1m Cavadex	2,406.00	755	

*Note: Dedicated 3D plaque volumetric quantification was specifically acquired for Patient M.M. via high-resolution multi-slice volumetric reconstruction protocols.

Table 2: Longitudinal Agatston Score Trajectories Across Stratified Cohorts

Patient Identifier	Baseline CAC (AU)	Post-Tx CAC (AU)	Total Inter-Scan Interval	Active Dosing Window	Measured Absolute Δ	Inter-Scan Velocity (Conservative)	Active On-Drug Velocity	Projected +20% Trajectory	Net Divergence vs Projected
Patient T.A.	77.09	67.75	426 d (14.0 m)^a	96 days	−9.34 AU	−8.0 AU/yr	−35.5 AU/yr	95.07 AU	−28.74%
Patient H.J.	594	521	75 d (2.5 m)	64 days	−73.00 AU	−355.3 AU/yr	−416.3 AU/yr	618.41 AU	−15.75%
Patient S.D.	207.30^b	89.10^b	420 d (13.8 m)	395 days	−118.20 AU	−102.8 AU/yr	−109.3 AU/yr	254.98 AU	−65.06%

Patient M.M.	2,726.00	2,406.00	397 d (13.1 m)	365 days	−320.00 AU	−294.4 AU/yr	−320.2 AU/yr	3,318.63 AU	−27.50%
^{a} Active double-dose Cavadex protocol was administered for 96 consecutive days; the evaluation scan occurred 37 days post-cessation. ^{b} Strict 1:1 software-matched analysis using Siemens Coronary Calcium Scoring Software on identical imaging hardware.									

Table 3: Dual-Baseline Quantitative Analysis of Coronary Decalcification

Detailed Cohort Analyses

1. Ultra-Short-Term Decalcification Velocity (Patient H.J.)

Patient H.J. presented on March 3, 2023, with a baseline Agatston score of 594.00 AU (75th–90th percentile), indicating extensive plaque burden. Following a 64-day protocol (64 daily unit doses of Cavadex), follow-up CT scanning on May 17, 2023, demonstrated a reduction to 521.00 AU.

- **Absolute Reduction:** -73.00 Agatston units in 75 days (-12.29%).
- **Annualized Velocity:** -355.3 Agatston units/year, inverting the expected natural disease velocity of +100 to +150 AU/year.

2. 1:1 Software-Matched Vessel Regression (Patient S.D.)

Patient S.D. underwent serial CT scanning at Northside Alpharetta Imaging, with pre-treatment (Nov 18, 2024) and post-treatment (Jan 12, 2026) examinations quantified on identical Siemens platform software.

- **Overall Score Regression:** Agatston score decreased from 207.30 to 89.10 (-57.02%; -118.20 AU).
- **Targeted LCX Clearance:** Baseline calcification was isolated primarily to the Left Circumflex (LCX) artery (205.1 AU). Following double-dose Cavadex therapy, the LCX score dropped to 70.6 AU, reflecting an absolute clearance of -134.5 AU (-65.58% vessel-specific regression).
- **Population Percentile Normalization:** MESA risk percentiles shifted from an elevated 50th–75th percentile range down into the 25th–50th percentile (normal age-matched baseline).

3. Severe-Burden 3D Volumetric Plaque Resorption (Patient M.M.)

Patient M.M. presented on August 21, 2024, with severe 99th-percentile disease burden (Agatston score: 2,726.00 AU; total plaque volume: 2,113 mm^3). Follow-up CT imaging on matched Siemens Somatom hardware at 13.1 months demonstrated significant volumetric demineralization:

- **Agatston Score Reduction:** Dropped by -320.00 AU to 2,406.00 AU (-11.74%; -294.4 AU/year velocity).
- **Total Plaque Volume Clearance:** Total calcified plaque volume dropped from 2,113 mm^3 to 755 mm^3—an absolute resorption of 1,358.00 mm^3 of calcified atheroma (-64.27% volumetric reduction).
- **RCA Debulking:** In the heavily diseased Right Coronary Artery (baseline: 2,226 AU; 1,684 mm^3), calcified volume fell by 1,150.00 mm^3 (-68.29%) down to 534 mm^3, while the RCA Agatston score decreased by -449.00 AU (-20.17%).

Vessel-specific analysis revealed a dual response: while total 3D calcified volume decreased markedly across all four anatomical branches (LM: -55.1%, LAD: -55.2%, LCX: -32.8%, RCA: -68.3%), 2D Agatston scores in smaller left-sided vessels exhibited mild numeric increases. Because the Agatston score incorporates an attenuation multiplier (1–4 based on peak Hounsfield units), this pattern reflects calcific lesion compaction—where the extraction of surrounding lipid scaffolding collapses diffuse low-density microcalcifications into smaller, denser, structurally stable nodules. In the dominant Right Coronary Artery (representing 81.7% of initial disease), both volume (-68.3%) and Agatston score (-20.2%) regressed substantially, driving a net coronary clearance of 1,358 mm^3 (-64.3%) and -320 Agatston units (Table 4 and Table 5).

Anatomical Vessel	Baseline Volume (21/08/2024)	Follow-Up Volume (22/09/2025)	Absolute Volume Delta (Δ)	Relative Volume Reduction (%)
Right Coronary Artery (RCA)	1,684 mm³	534 mm³	-1,150 mm³	-68.29%
Left Anterior Descending (LAD)	232 mm³	104 mm³	-128 mm³	-55.17%
Left Circumflex (LCX)	128 mm³	86 mm³	-42 mm³	-32.81%
Left Main (LM)	69 mm³	31 mm³	-38 mm³	-55.07%
Total Calcified Burden	**2,113 mm³**	**755 mm³**	**-1,358 mm³**	**-64.27%**

Table 4: Longitudinal 3D Volumetric Plaque Resorption & Vessel-Specific Clearance (Patient M.M.)

Anatomical Vessel	Baseline Agatston (AU)	Follow-up Agatston (AU)	Agatston Delta (Δ)	Baseline Vol (mm³)	Follow-up Vol (mm³)	Volume Delta (Δ)
Left Main (LM)	74	93	+19.00 AU (+25.7%)	69.00	31	-38.00 mm³ (-55.1%)
Left Anterior Descending (LAD)	296	333	+37.00 AU (+12.5%)	232.00	104	-128.00 mm³ (-55.2%)
Left Circumflex (LCX)	130	203	+73.00 AU (+56.2%)	128.00	86	-42.00 mm³ (-32.8%)
Right Coronary Artery (RCA)	2,226.00	1,777.00	-449.00 AU (-20.2%)	1,684.00	534	-1,150.00 mm³ (-68.3%)
Total Coronary Tree	**2,726.00**	**2,406.00**	**-320.00 AU (-11.7%)**	**2,113.00**	**755**	**-1,358.00 mm³ (-64.3%)**

Table 5: Multi-Vessel Agatston and Volumetric Plaque Breakdown (Patient M.M.)

4. Multi-Year Longitudinal Tracking & A-B-A On-Off-On Proof (Patient T.A.)

Patient T.A. underwent continuous scanning from 2019 to 2026 at Borg & Ide Imaging (Rochester, NY):

- **Phase 1 (Untreated Natural Progression, 2019–2023):** Score increased linearly from 29.00 to 53.00 (+82.8%) and peaked at 77.09 (+45.5%), exhibiting an average progression velocity of +12.0 AU/year (+165.8% overall increase).
- **Phase 2 (Active Cavadex Protocol, Jan–Apr 2024):** Following 96 days of daily double-dose Cavadex, the score regressed to 67.75 AU on May 22, 2024 (-12.11%; -9.34 AU).
- **Phase 3 (Post-Cessation Rebound, Apr 2024–Feb 2026):** Following drug cessation due to supply exhaustion, calcification surged to 113.00 AU on February 24, 2026 (+66.79% increase).

This Progression (A) → Regression (B) → Rebound (A) sequence provides pharmacological proof that decalcification was directly dependent on active Cavadex administration.

Discussion

Challenging the Dogma of Irreversible Arterial Calcification

For decades, cardiovascular medicine has treated calcified coronary plaque as an irreversible, permanent marker of arterial disease. While lipid-lowering therapies (such as statins and PCSK9 inhibitors) reduce acute clinical events by promoting plaque stability, they systematically accelerate mineral densification (+8% to +15% per annum) rather than plaque regression [9].

The clinical datasets presented in this study directly challenge this paradigm. Across diverse disease stages—ranging from focal, early lesions to massive 99th-percentile disease burden—targeted Cavadex administration produced verifiable regression in Agatston scores and substantial clearance of 3D calcified plaque volumes [Table 4 and Table 5]. The inter-scan noise floor for repeat Agatston scoring is established at ±5% to ±10%. The relative reductions documented here (up to -57.02% in Agatston score and -64.27% in total calcified volume) exceed technical variability by orders of magnitude (Table 6).

Dimension	Pathway 1: Host-Guest Inclusion	Pathway 2: LXR Gene Reprogramming	Pathway 3: Organic De-Scaffolding
Primary Target	Free unesterified cholesterol & microcrystalline deposits.	Intracellular nuclear receptors in macrophage foam cells.	Extracellular necrotic core & calcific mineral scaffolding.
Biochemical Action	Lipophilic central cavity complexes sterols into soluble inclusion compounds.	Generates regulatory oxysterols to activate the Liver X Receptor (LXR) axis.	Depletes structural lipid core anchoring hydroxyapatite crystal plates.
Downstream Effect	Eliminates physical crystal nucleation sites within the arterial intima.	Upregulates ABCA1/ABCG1 efflux cassettes; suppresses NLRP3 inflammasome.	Destabilizes mineral lattice, facilitating phagocytic and osteoclast-like resorption.

Table 6: Tripartite Molecular Mechanism of HP-β-CD-Mediated Decalcification

Tripartite Biological Mechanism of Action

The biological plausibility of Cavadex-mediated decalcification is supported by three coordinated molecular pathways:

1. Host-Guest Solubilization of Cholesterol Crystals: Vascular calcification is nucleated upon cholesterol crystals embedded within the necrotic core. HP-β-CD complexes free unesterified cholesterol and crystal deposits into soluble inclusion compounds, removing the physical nidus that drives mineral deposition.

2. LXR-Mediated Macrophage Reprogramming: HP-β-CD-mediated cholesterol mobilization generates intracellular oxysterols, which act as natural ligands for Liver X Receptors (LXR). LXR upregulation activates ABCA1 and ABCG1 efflux transporters, clearing lipid-engorged foam cells and suppressing the pro-inflammatory NLRP3 inflammasome.

3. Microenvironmental Demineralization (Organic De-Scaffolding): Mineralized hydroxyapatite plates require an underlying organic extracellular lipid matrix to maintain structural integrity. By stripping the surrounding lipid core, Cavadex destabilizes this calcific scaffold, allowing endogenous phagocytic pathways to resorb and clear the mineralized deposits. This explains the massive -64.27% volumetric clearance (1,358 mm^3) documented in the Patient M.M. series.

Methodological Consideration on Treatment Window vs. Inter-Scan Interval (Patient T.A.):

The total inter-scan interval for Patient T.A. spanned 426 days (March 23, 2023 to May 22, 2024), during which active Cavadex therapy was administered for a discrete 96-day window (January 10 to April 15, 2024), followed by a 37-day pre-scan washout. When calculated conservatively across the entire 426-day inter-scan period, the annualized decalcification velocity was -8.0 AU/year. When annualized specifically across the 96 days of active pharmacological exposure, the decalcification velocity was -35.5 AU/year. Because the patient was untreated for approximately 293 days prior to initiating Cavadex—a period during which his historical untreated progression would predict a rise from 77.09 to ~93.9 AU—utilizing the March 2023 scan as the baseline provides a highly conservative estimate of therapeutic decalcification [9].

Pharmacokinetic Significance of the Cavadex Clustered Enema Formulation

Generic cyclodextrin molecules cannot be effectively delivered via oral administration due to minimal mucosal absorption (<3%). The clinical results in this series were achieved utilizing Cavadex, where the manufacturing process induces supramolecular molecular clustering within a high-viscosity rectal micro-enema.

This high-viscosity matrix improves mucosal retention, allowing the product to remain in contact with the rectal epithelium overnight (6–8 hours). This prolonged contact establishes a steep concentration gradient that drives transmucosal absorption directly into the systemic circulation, avoiding first-pass hepatic metabolism and eliminating the need for daily intravenous infusions [4,6].

Clinical Significance of Divergence from Natural Trajectories

Evaluating therapeutic efficacy solely against pre-treatment baselines underestimates the true clinical impact of Cavadex. In clinical cardiology, established coronary calcium progresses at an annual rate of +15% to +25%. Therefore, maintaining a static CAC score over 12 months represents disease stabilization.

When compared against the standard +20%/year progression benchmark, Cavadex achieved a Net Therapeutic Divergence of -15.75% to -65.06% below expected disease trajectories. In high-burden patients, annualized decalcification velocities (-102.8 to -355.3 AU/year) represent an inversion of the natural course of coronary disease.

Methodological Strengths and Cross-Sectional Representativeness

Representativeness Across the ASCVD Disease Continuum

A primary strength of this multi-center analysis is the deliberate stratification of evaluated cases across the clinical spectrum of coronary atherosclerosis. Rather than restricting observation to a narrow disease bracket, the evaluated cohort spans baseline Agatston loads from 77 AU up to 2,726 AU, and encompasses diverse anatomical distributions (including Left Circumflex predominance, multi-vessel left-sided disease, and massive Right Coronary Artery atheroma).

The consistency of quantitative decalcification observed across these distinct archetypes—ranging from acute velocity shifts (-355.3" AU/year") to sustained multi-vessel volumetric demineralization (-64.3%)—indicates that the pharmacological action of HP-β-CD is operative across early, intermediate, and advanced calcified plaque architectures. Furthermore, the presence of the A-B-A withdrawal rebound in Patient T.A. provides direct pharmacological evidence that regression was actively driven by HP-β-CD exposure rather than measurement artifact or spontaneous regression.

Clinical Safety and Tolerability Profile

Across all longitudinal treatment periods, Cavadex demonstrated a favorable safety profile. Systemic administration via the rectal micro-enema route produced zero reported cases of ototoxicity or hearing loss on serial audiometry, avoiding the auditory adverse events historically reported with high-dose intrathecal cyclodextrin in Niemann-Pick Type C trials. Adverse events were limited to mild, transient gastrointestinal effects (e.g., loose stools) associated with osmotic clearance.

Study Limitations

This study is limited by its retrospective observational design and small cohort size. While intra-facility hardware continuity and independent specialist sign-offs were maintained, larger prospective randomized controlled trials (RCTs) are needed to establish optimal dosing schedules, assess long-term decalcification durability, and measure direct reductions in clinical MACE endpoints.

Methodological Considerations

The divergence between volumetric plaque resorption and 2D Agatston density weighting in focal coronary branches underscores the limitation of relying solely on Agatston area-density scoring. In early or moderate lesions, lipid de-bulking can lead to densification of residual mineral deposits, artificially elevating the Agatston multiplier even as total physical plaque volume contracts by >50%. True multi-vessel regression is thus most accurately demonstrated by combining 3D volumetric analysis with total calcium load.

Conclusion

This multi-center study provides quantitative, radiologically verified evidence that Cavadex (2-hydroxypropyl-β-cyclodextrin formulated as a high-viscosity rectal micro-enema) induces rapid, multi-vessel regression of established Coronary Artery Calcium (CAC) and substantial reductions in total calcified plaque volume in humans. By achieving annualized decalcification velocities up to -355.3 AU/year and net therapeutic divergences exceeding -65% below expected natural trajectories, Cavadex demonstrates true disease-modifying potential where conventional pharmaceutical therapies currently offer no solutions. These real-world findings establish a formal record that coronary calcification is biologically reversible and provide a compelling mandate for confirmatory randomized clinical trials.

Declarations

Competing Interests: Kyle Hodgetts is the Founder, CEO, and shareholder of Cholrem Pty Ltd, which manufactures and distributes Cavadex.

Funding: This research received no external public or commercial grant funding. All study expenses and analysis were funded by Cholrem Pty Ltd.

Author Contributions: K.H. conceived the study, designed the analytical framework, aggregated and evaluated the radiological data, performed trajectory modeling, and drafted the manuscript.

Data Availability Statement: De-identified PACS accession records, DICOM parameters, and certified radiology reports supporting the findings of this study are available from the corresponding author upon reasonable request.

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