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Targeting the reduction of inflammatory risk associated with cardiovascular disease by treating periodontitis either alone or in combination with a systemic anti-inflammatory agent: protocol for a pilot, parallel group, randomised controlled trial

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ABSTRACT

Introduction Cardiovascular disease (CVD) is associated with systemic inflammation. Colchicine, an anti-inflammatory drug, reduces the incidence of CVD events. Periodontitis, a chronic localised inflammatory disease of the tissues supporting the teeth, triggers systemic inflammation and contributes to inflammatory risk. Treatment for periodontitis reduces markers of inflammation, however, there is no evidence on whether an anti-inflammatory medication in combination with periodontal treatment can reduce the inflammatory risk. The aim of this trial is to investigate the effect of periodontal treatment either alone or in combination with an anti-inflammatory agent on inflammation in patients with periodontitis and CVD at 8 weeks.

Methods and analysis 60 participants with moderate-to-severe periodontitis, coronary artery disease and an increased inflammatory risk (>2 mg/L high sensitivity C reactive protein (hsCRP) levels) will be recruited from a tertiary referral hospital in Australia in a parallel design, single blind, randomised controlled trial. Baseline hsCRP levels, lipid profile and periodontal assessment will be completed for each participant before they are randomised in a 1:1:1:1 ratio to one of 4 arms as follows: (group A) periodontal treatment and colchicine; (group B) periodontal treatment only; (group C) colchicine only or (group D) control/delayed periodontal treatment. Periodontal treatment will be provided over three treatment visits, 0.5 mg of colchicine will be provided as a daily tablet. Participants will be followed up at 8 weeks to measure primary and secondary outcomes and complete a follow-up questionnaire. The primary outcome is the difference in hsCRP levels, the secondary outcomes are differences in lipid levels and periodontal parameters and the feasibility measures of recruitment conversion rate, completion rate and the safety and tolerability of the trial.

Ethics and dissemination The study has been approved by the Western Sydney Local Health District Human Ethics Committee (protocol number 2019/ETH00200). Results will be published in peer-reviewed journals and presented at conferences.

Trial registration number ACTRN12619001573145.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ This is the first study to investigate changes in a systemic inflammatory marker in patients with cardiovascular disease using anti-infective and anti-inflammatory treatment (treatment of gum disease) either alone or in combination with a systemic anti-inflammatory medication.
⇒ The suitability of a self-report questionnaire for recruiting participants with periodontitis from a cardiology ward will be tested and will provide a blueprint for a future multicentre study.
⇒ The feasibility of the recruitment conversion rate and study completion rate will be established using prespecified feasibility targets.
⇒ The design of a pilot study implies that findings cannot be used to make conclusions about the effectiveness of the interventions on reducing systemic inflammation.
⇒ Due to the nature of the clinical intervention, it is not possible to blind those delivering or receiving the intervention.

INTRODUCTION

Periodontitis

Periodontitis is a chronic microbial infection of the soft and hard tissues supporting the teeth.[1] The prevalence of periodontitis ranges from 30% to 55%, increases with age and peaks in the fifth and sixth decades of life.[2 3] The chronic inflammatory response in periodontitis is triggered by persisting subgingival bacterial deposits, is slowly progressive

and in most cases painless.[4] Untreated, periodontitis can result in the loss of supporting bone and connective tissue around the teeth leading to the loosening of teeth and eventually tooth loss.[4] The consequences of periodontitis may impair the quality of life and may cause psychological distress due to compromised aesthetics, and reduced chewing function.[5]

Coronary artery disease and inflammation

The pathophysiology of atherosclerosis was traditionally attributed to an increase in lipid deposits on the surface of artery walls resulting in a decrease or complete occlusion of blood flow triggering a cardiovascular incident such as a myocardial or cerebral infarction.[6] There is growing evidence that inflammation plays a key role in all stages of atherosclerosis, from the formation of the early lesion through to thromboembolism.[7] The elevation of inflammatory markers, in particular C reactive protein (CRP), is associated with an increased risk of atherosclerosis,[8] and in survivors of myocardial infarction (MI) an increased risk of recurrent infarction and death due to coronary heart disease (CHD).[9] Therefore, reducing this inflammatory risk is integral to improving cardiovascular disease (CVD) related outcomes.

Reducing systemic inflammation

The Canakinumab Anti-inflammatory Thrombosis Outcome Study demonstrated that targeting inflammation, via direct inhibition of interleukin-1β in survivors of acute MI with elevated CRP levels ≥2 mg/L, resulted in a modest reduction in major adverse CVD events.[10] However, canakinumab is not a cost-effective treatment and serious adverse events (SAEs) such as sepsis and fatal injection were reported in this trial.[10] Another anti-inflammatory medication to reduce CVD events is colchicine, an anti-tubulin drug commonly used in the treatment of gout. Colchicine has a broader mechanism of action compared with canakinumab and includes inhibition of tubulin polymerisation, resulting in downregulation of inflammatory pathways and alteration of leucocyte responsiveness.[11] Colchicine has been specifically shown to reduce levels of high sensitivity CRP (hsCRP),[12] which is an established marker for future CVD events.[13] In addition, randomised controlled trials (RCTs) of low-dose colchicine (0.5 mg) in patients with chronic coronary artery disease in the Low-Dose Colchicine trial and the Colchicine Cardiovascular Outcomes trial have shown that although colchicine reduces the overall risk of cardiovascular events in MI survivors, a significant effect on death from cardiovascular causes or MI was not shown.[14 15] Interestingly, non-specific anti-inflammatory treatment with methotrexate in the cardiovascular inflammation reduction trial has been shown to have no effect on cardiovascular outcomes or reduce inflammatory markers.[16] The evidence, therefore, does not yet support routine administration of anti-inflammatory medications as secondary prevention for CVD and raises the question about whether an intervention further upstream maybe warranted.[17]

Although the impact of colchicine on hsCRP is well established, the impact on lipids is inconclusive. A study on short term exposure (30 days) to colchicine failed to demonstrate a significant impact on lipid levels in patients with chronic coronary artery disease.[18] However, in a rodent model of diet induced hyperlipidaemia, 5 weeks of colchicine treatment has been shown to reduce plasma lipids.[19] There is therefore a need for further clinical research.

Periodontal therapy is aimed at reducing inflammation and there is moderate evidence to support the reduction of serum inflammatory markers such as CRP following treatment for periodontitis.[20] Although the evidence to date does not suggest that periodontal therapy reduces plasma lipids.[20] Periodontitis has been shown to be associated with dyslipidaemia, therefore, further clinical studies on the impact of periodontal treatment on plasma lipids is indicated.[21]

Biological mechanisms linking periodontitis and coronary artery disease

Periodontitis, a localised chronic inflammatory response in the oral cavity, is associated with an increased risk of atherosclerosis and an increase in systemic inflammatory markers.[22] Oral bacteria enter the blood stream directly as a result of a transient bacteraemia arising during normal daily activities such as eating, tooth brushing or flossing[23] and may lodge on artery walls triggering atherogenesis.[24] In animal models, pathogenic oral bacteria associated with periodontitis have been identified in atherothrombotic tissues and have been shown to induce endothelial dysfunction.[25] In addition, some pathogenic oral bacteria are able to invade host phagocytes, allowing the bacteria to be transported to distant organs causing atheroma formation in these sites once they are deposited by the phagocyte.[26] Finally, periodontitis has been shown to trigger an acute phase response leading to the systemic release of inflammatory markers, including CRP.[24]

Periodontal treatment studies

Observational studies have demonstrated that periodontitis is consistently associated with a moderately increased risk for coronary artery disease[27–29] and that this association is dose-dependent, with more severe forms of periodontitis associated with an increased risk for CVD.[28] Systematic reviews of interventional studies in 2014[22] and 2018[30] have confirmed the impact of periodontal treatment on reducing inflammatory markers including CRP. Furthermore, a recent narrative review reported that multiple RCTs have demonstrated that periodontal treatment, or periodontal treatment with adjunctive aids such as antibiotics reduce inflammatory markers and circulating lipids.[31]

With the increasing interest for the treatment of CVD by anti-inflammatory medications and the well-documented positive effect of periodontitis treatment

on systemic hsCRP levels, there is interest in comparing the effect of both dental and oral anti-inflammatory treatment on CRP levels. The fact that periodontitis treatment has no adverse systemic side effects, compared with those reported for canakinumab orcolchicine makes it an attractive treatment option for reducing the systemic inflammatory burden. To prepare for a novel randomised clinical trial using combined endpoints of CVD this feasibility study is essential to test recruitment, establish sample size and trial safety for a definitive study investigating how periodontitis treatment alone or in combination with a systemic anti-inflammatory drug reduces systemic CRP levels.

The primary objectives of this pilot RCT are to determine the changes in hsCRP levels, between baseline and the 8-week follow-up. In addition, this study will determine changes in lipids and periodontal parameters between baseline and 8-week follow-up and will evaluate the feasibility of recruitment conversion, trial completion, and the safety and tolerability of trial interventions.

For the future RCT, we hypothesise that periodontitis is an upstream source of inflammatory risk, and that, non-surgical periodontal treatment is an upstream approach that can reduce systemic inflammation and the combined events of CVD. In addition, we hypothesise that periodontal treatment in combination with colchicine will result in a greater decrease in hsCRP than either treatment modality on its own.

METHODS AND ANALYSIS

Study design and setting

This study is a parallel design, single blinded, pilot RCT with an 8-week follow-up investigating the effect of periodontal treatment and colchicine therapy on reducing systemic inflammation (hsCRP). The study will be conducted at Westmead Hospital and the Westmead Centre for Oral Health, both of which are a part of the Western Sydney Local Health District in New South Wales, Australia. The design and methods of this trial comply with the Consolidated Standards of Reporting Trials statement for RCTs.[32] Participants will be recruited from the cardiology ward at Westmead Hospital and periodontal treatment (three dental visits over a 2-week period) will be provided in a general practice dental clinic at the Westmead Centre for Oral Health. The first participant for this study was recruited on 23 June 2022 and we expect the study to be completed in 12 months.

Study population

A total of 60 participants will be recruited from a cardiology ward within a tertiary teaching hospital in Sydney, Australia. Participants will be screened by staff in the cardiology ward for medical eligibility (adult (≥ 18 years), have acute coronary syndrome/stable angina as documented in the medical record, currently on statin therapy and have hsCRP>2 mg/L). Screening for dental eligibility criteria will be a two-step process, the first part will be performed in the cardiology ward using a self-report oral health related questionnaire.[33] Participants are eligible if they have ≥15 teeth, have not received treatment for their gums (subgingival scaling and root planning) in the last 6 months and have moderate to severe periodontitis (≥20 periodontal pockets with probing pocket depths of >4 mm and marginal alveolar bone loss of >30%).[34] A study researcher will ensure that eligibility criteria are satisfied before the participant is invited for a clinical periodontal analysis, which will determine the periodontal diagnosis and thereby complete the screening process and form part of the baseline assessment. Table 1 provides a summary of the eligibility criteria. A sequence of the recruitment process is provided in figure 1.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Medical	▶ ≥18 years. ▶ Coronary artery disease (acute coronary syndrome/stable angina documented in medical records). ▶ Current statin therapy. ▶ hsCRP >2 mg/L.
	Dental	▶ ≥15 teeth. ▶ Not treated for gum disease (subgingival scaling and root planning) in the last 6 months. ▶ Moderate to severe periodontitis.[34]
Exclusion criteria	Medical	▶ Current or recent antibiotic therapy in the (last 3 months). ▶ Pregnant, lactating of planning pregnancy. ▶ Severe renal impairment: Glomerular filtration rate (GFR) <30. ▶ Severe hepatic impairment: History of CKD and or alanine aminotransferase >3 upper limit of normal. ▶ Blood dyscrasias. ▶ Taking medications that interact with colchicine.

hsCRP, high sensitivity C reactive protein.

Randomisation

Randomisation will be stratified by age, gender and periodontal status as measured by the Periodontal Screening and Recording index (PSR). A randomisation allocation table will be computer generated and Research Electronic Data Capture (REDCap), a secure web-based password protected software platform will be used for allocation of participants to each group. Participants will be contacted by an email, which will be automated and sent through REDCap to advise them when to attend their treatment visit. Participants will be randomised in a 1:1:1:1 ratio into one of four arms of the trial. Allocation will occur after baseline assessment and the researcher conducting both the baseline and follow-up assessment will be blinded to group allocation. It is not possible to blind the participant or the treating dentist due to the nature of the dental treatment.

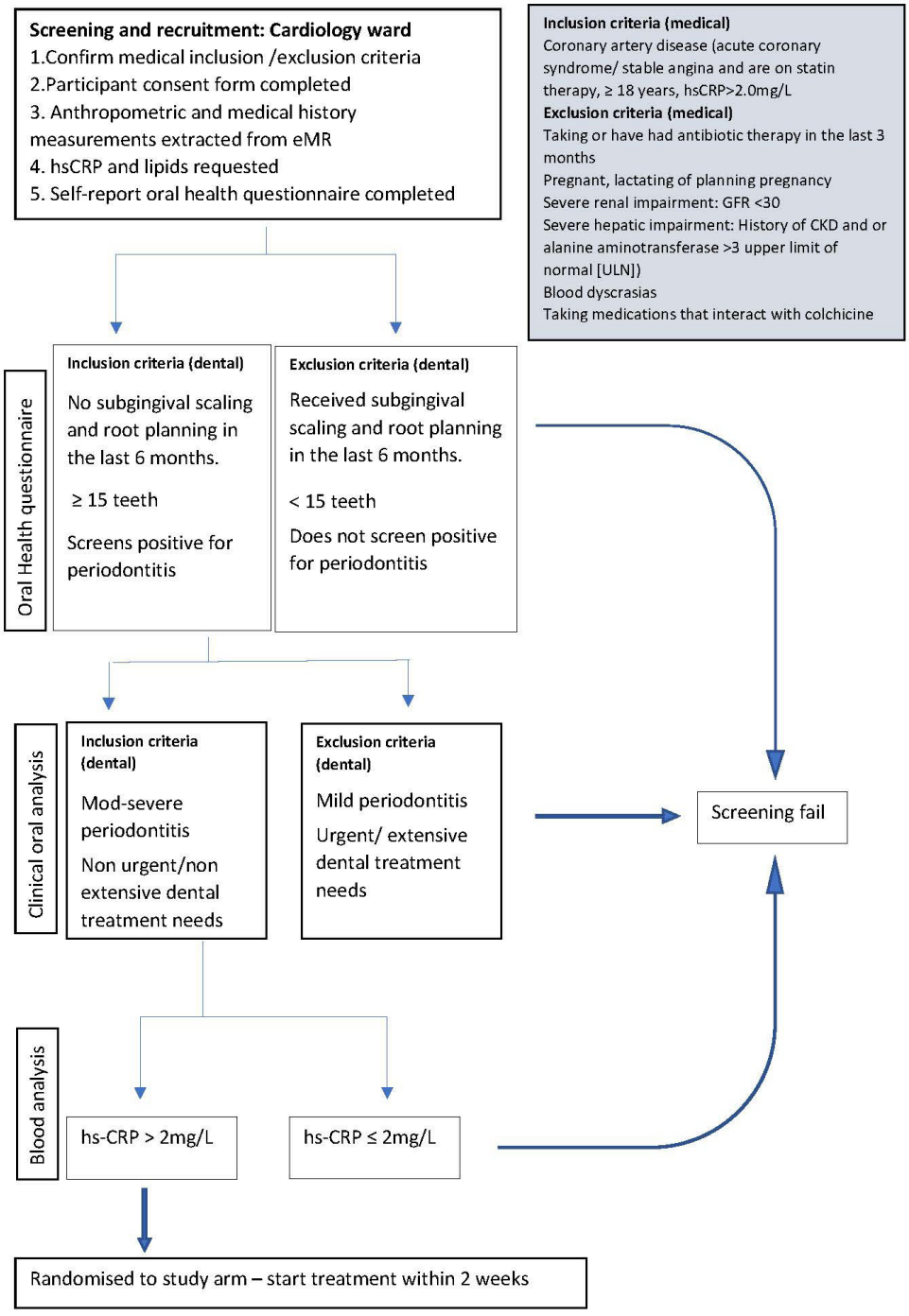

Figure 1 Summary of the recruitment process. Participants are screened in the cardiology ward to ensure they meet the medical inclusion/exclusion criteria, informed consent is signed prior to the completion of the self-report oral health questionnaire. If the questionnaire indicates a risk for periodontitis the participant will be invited to attend a baseline assessment which will include an oral examination, anthropometric and medical history measures will be recorded and blood tests will be arranged. If the participant satisfies the dental inclusion/exclusion criteria they will be randomised to the treatment arms. High sensitivity C reactive protein (hsCRP), glomerular flitration rate (GFR), chronic kidney disease (CKD), electronic medical record (eMR).

Interventions

Participants will be randomised into one of four arms as follows: (group A) periodontal treatment and colchicine; (group B) periodontal treatment only; (group C) colchicine only or (group D) control/delayed periodontal treatment. Treatment for the periodontal treatment groups (groups A and B) will be initiated within 2 weeks from randomisation and will be provided by a dentist over three treatment visits during weeks 1 and 2 of the study period. Similarly, colchicine treatment for the colchicine treatment groups (groups A and C) will be provided as a 0.5 mg daily tablet for 8 weeks of the study period. The

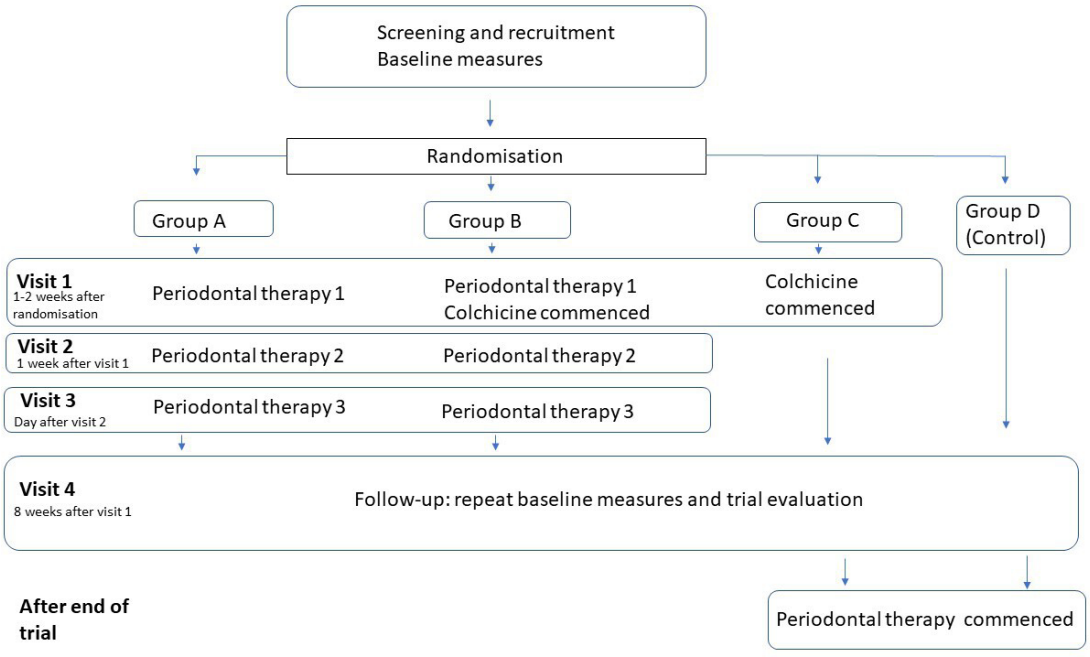

Figure 2 Study flow chart.

control group and colchicine only group (groups C and D) will receive periodontal treatment after the 8-week follow-up (figure 2). A single calibrated and trained oral health therapist, blinded to the treatment allocations will perform the baseline and 8-week follow-up assessments.

Non-surgical periodontal treatment

Periodontal treatment will be provided as three treatment visits. Visit 1 will include oral hygiene motivation and instruction and supragingival plaque removal. Visit 2 will occur 1 week after visit 1 and will include subgingival instrumentation on one side of the mouth. Subgingival treatment will be provided under local analgesia and will involve a combination of powered ultrasonic and hand instrumentation with no limit set to the duration of the session. Visit 3 will occur on the following day, as per the two-stage (within 24 hours) full-mouth protocol[35] and will include subgingival instrumentation on the other side of the mouth. A final follow-up visit will be completed 8 weeks after visit 1 to repeat the baseline measures. Participants who fail to attend a treatment visit will be followed up by phone and the reason for non-attendance will be documented. All non-surgical periodontal treatment will be provided by trained dental professionals following standard treatment guidelines and standardised operating procedures.[35]

Anti-inflammatory treatment

Colchicine treatment will be provided to participants as a 0.5 mg tablet to be taken orally once/day for 8 weeks. A study designated doctor will prescribe the colchicine and the drug will be dispensed free of charge by a private pharmacy located within Westmead Hospital according to the study protocol. Participants will be asked to keep a logbook to record daily intake. Compliance will be ascertained through a pill count by the number of tablets that are returned to the pharmacy at the end of the study period.

Study outcomes and data collection

Participants will be followed up at 8 weeks to measure primary and secondary outcomes. The primary outcome of this pilot trial is the difference in hsCRP measures. Secondary outcomes are the differences in lipid levels and periodontal parameters and the feasibility measures. The trial has been designed to estimate the proportion of patients who meet our feasibility criteria with reasonable confidence.[36 37] The study would proceed to a definitive trial without modification if these prespecified feasibility criteria are met, including recruitment conversion rate and completion rate. In addition, the trial will report time to recruitment and safety and tolerability of the trial.

Assessment of physical measures

Physical and anthropometric measurements will be recorded by the nursing staff in the morning before the participants' first meal and will include weight (kg), height (cm), heart rate (beats/minute) and blood pressure (mm Hg). Weight measurements will be taken using electronic scales, the participant will be required to wear minimal clothing and remove their shoes. Height measures will be taken using a stadiometer with shoes removed. Heart rate and blood pressure measures will be recorded with an automated machine by trained nursing staff while the participant is seated and rested. Body mass index will be calculated using the measures of height and weight.

Table 2 Clinical parameters for periodontal analysis

Clinical parameter	Description
Recession	Distance in mm from the cemento enamel junction to the gingival margin.
Probing pocket depth	Distance in mm from the gingival margin to the base of the sulcus or pocket.
Clinical attachment level	Distance in mm from the cementoenamel junction to the base of the sulcus or pocket.
Bleeding on probing	The presence of bleeding expressed as yes/no at each site (30 s after probing).
Plaque and bleeding index	The presence of plaque deposits and gingival bleeding will scored using established indices.[46 47]

Assessment of inflammatory burden: change in hsCRP and lipid profile

Two fasted 10 mL venous blood samples will be collected from the antecubital vein by a registered nurse from participants at baseline and follow-up. The blood samples will be sent for analysis of hsCRP to a laboratory at the Royal Prince Alfred Hospital, Sydney and for lipid profile analysis (total cholesterol, triglycerides, low-density lipoprotein cholesterol and high-density lipoprotein cholesterol) to a laboratory at Westmead Hospital. The hsCRP analyses will be conducted on a Cobas 8000, modular analyser and the lipid profile will be analysed on a Siemens Atellica immnunoassay and clinical chemistry analyzer.

Assessment of clinical oral health measures: change in periodontal parameters

All clinical parameters will be recorded at six sites per tooth (distobuccal, mid-buccal, mesiobuccal, distopalatal, mid-palatal, mesiopalatal) using a Florida probe[38] (table 2).

For each participant the following information will be reported: (A) number of teeth, (B) mean periodontal pocket depth, (C) mean clinical attachment level, (D) the percentage of sites with probing pocket depths of 1–3 mm, 4–6 mm and >7 mm, (E) the percentage of sites with BOP, (F) periodontal stage and grade, (G) plaque and bleeding indices and (H) tooth brushing and interdental cleaning frequency.

Assessment of feasibility measures

The proportion of participants successfully recruited to the trial and the proportion of participants successfully completing the trial will be compared with our prespecified feasibility criteria.

In addition, we will report the percentage of participants lost as screening failures and the reasons for screening failure will be identified. The time taken for recruitment will also be provided. The percentage of participants starting treatment within 1–2 weeks of randomisation will be reported, and a breakdown of the proportion of participants completing each treatment visit along with reasons for non-completion provided.

Assessment of participant safety and tolerability of the trial

At the end of the 8-week period, participants will be invited to complete a structured questionnaire of a series of Likert responses and open-ended questions on their experiences in the trial. Participants will be asked to rate the acceptability of the study procedures, how likely they are to recommend the trial to others and for details of any AEs following treatment interventions including the severity of any post-treatment complications.

Process evaluation

A screening log will be kept in order to record reasons for non-participation for individuals who are either ineligible or who decline to participate. The screening log will also record the number of participants recruited each week and the time taken to complete recruitment. A treatment log will be kept in order to record timing of first treatment visit following randomisation and any reasons for delays, missed treatment visits and reasons for any non-attendance of treatment visits or non-compliance with medications. To assess the safety of the trial, data on AEs and SAEs will be collected at treatment visits and at the final 8-week follow-up visit as part of the treatment log. Participants will be asked non-leading questions to determine whether they have developed a new medical or dental condition or have an exacerbation of an existing medical or dental condition.

Statistical analysis plan

The statistical plan for this study will be determined prior to study completion. Analysis of the difference in hsCRP, lipids and periodontal parameters will be according to the intention-to-treat principle where participants are analysed in the arm they have been allocated. The level of statistical significance will be set at $p<0.05$. The primary analysis will be an adjusted analysis performed to assess differences between groups for hsCRP, lipid profile and periodontal parameters between baseline and follow-up using log binomial for binary (categorical) outcomes and an analysis of variance for continuous outcomes. Covariates used for adjusted analyses will include age, sex, PSR code, smoking status, periodontal stage and number of teeth. Outcome measures available at baseline (hsCRP, lipid profile and periodontal parameters) will also be included in the statistical model. An unadjusted analysis will be performed to assess differences between groups using a X^2 test for binary (categorical) outcomes and independent sample t-tests for continuous outcomes.

The feasibility measures will be presented as percentages, and means and SD, as is appropriate. The outcomes will be compared with the predetermined feasibility criteria to determine whether changes to the protocol are required before proceeding with the multicentre trial.

Sample size

This pilot study is not powered to determine the impact of periodontal treatment and/or colchicine treatment on systemic inflammation, this question will be answered in

a larger definitive trial. The sample size of 15 per arm for this study has been chosen based on pilot study recommendations when no prior studies exist on which to base the sample size calculation and includes provision for a 20% attrition rate.[39] The data from this study will be used to estimate variance to enable sample size calculation for the main trial.

The feasibility criteria for this study have been designed as follows:

1. Recruitment conversion rate—we estimate that as the prevalence of periodontitis in a cardiovascular population can be as high as 97%[40] and that over 40% of patients with CHD have been shown to have elevated hsCRP levels.[41] We estimate a rate of 40% successful screening, therefore a sample size of 60 has a 95% CI of (32.2% to 47.8%).
2. Completion rate—based on colchicine related side effects, which has led to 10%–15% of patients withdrawing from a previous trial[42] and approximately 15% of participants failing to comply with multiple treatment visits in a periodontal therapy trial,[43] for an estimated completion rate of 70%, a sample size of 60 has a 95% CI of (58.41% to 81.59%).

Data management

Study data will be collected and stored using REDCap tools hosted at the University of Sydney.[44 45] Access to the REDCap data base will be controlled by the principal investigator and will require institutional log in credentials. For data analysis, data files will be stored on the University of Sydney Research Data Store, which is a secure platform hosted by the University for research data storage. Access to these data files will be controlled by the principal investigator and will require institutional log in credentials. Deidentified data will be used for any analyses and publications and data will be retained for a period of 5 years following study completion.

Patient and public involvement

Participant feedback from the trial evaluation survey and information collected in relation to the safety and tolerability of the trial will provide important patient involvement in the design of a future trial multicentre trial.

ETHICS AND DISSEMIATION

Ethical approval

The study sponsor is the Western Sydney Local Health District. The design and conduct of this trial will be overseen by a study team (authors) from the University of Sydney's Westmead Applied Research Centre. The sponsor will not be involved in collection, management or analysis of the data. The study will comply with the National Health and Medical Research Council ethical guidelines for human research. Ethical approval for this trial has been obtained from the Western Sydney Local Health District Human Research Ethics Committee (protocol number: 2019/ETH00200), protocol version 7 dated 19 July 2022. Written informed consent will be obtained from all participants (online supplemental material 1) before any data collection or intervention occurs. Study findings are intended to inform the design of a larger, definitive trial. The trial registration number is ACTRN12619001573145 and has been registered prospectively (14/11/2019) with the Australian and New Zealand Clinical Trials Registry (ANZCTR) (refer to online supplemental material 2) for trial data set). A clinical trials notification (CTN) for this study has been obtained from the Therapeutic Goods Administration (CT-2021-CTN-03 319-1 v1). The study has been funded Internally by the University of Sydney.

Dissemination

The results from this study will be published in peer-reviewed journals and presented nationally and internationally at both oral health and cardiology conferences. Individual participant data will be made available after deidentification, beginning 9 months and ending 5 years after publication of the results, to researchers who provide a methodologically sound proposal. The outcomes from this pilot trial will be used to refine the study protocol, establish a sample size and will allow for planning of a larger multicentre trial.

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Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

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Participant Information Sheet/Consent Form

Interventional Study - *Adult providing own consent*

Westmead Hospital

Title	Reducing the systemic inflammation associated with periodontitis to reduce risk in patients with coronary artery disease and on statin therapy- a randomised feasibility study
Short Title	Periodontitis and coronary artery disease
Protocol Number	2019/PID00206
Project Sponsor	WSLHD
Coordinating Principal Investigator	Professor Clara Chow
Principal Investigator	Dr Rahena Akhter
Associate Investigator(s)	Professor Joerg Eberhard.
Location	Westmead Hospital

Part 1 What does my participation involve?

1 Introduction

You are invited to take part in this research project because you have coronary artery disease and are currently on statin therapy. The purpose of this research project is to test whether therapy of gum disease reduces the risk of having a cardiovascular incident, such as a heart attack or a stroke.

This Participant Information Sheet/Consent Form tells you about the research project. It explains the tests and treatments involved. Knowing what is involved will help you decide if you want to take part in the research.

Please read this information carefully. Ask questions about anything that you don't understand or want to know more about. Before deciding whether or not to take part, you might want to talk about it with a relative, friend or your local doctor.

Participation in this research is voluntary. If you don't wish to take part, you don't have to. You will receive the best possible care whether or not you take part.

If you decide you want to take part in the research project, you will be asked to sign the consent section. By signing it you are telling us that you:
- Understand what you have read
- Consent to take part in the research project
- Consent to have the tests and treatments that are described
- Consent to the use of your personal and health information as described.

You will be given a copy of this Participant Information and Consent Form to keep.

2 What is the purpose of this research?

Health professionals have long established a link between gum disease and cardiovascular disease. However, whether the treatment of gum disease reduces the risk of having a cardiovascular incident, for example- a heart attack, remains a questions mark.

Colchicine is a drug that has been shown to reduce cardiovascular risk. This trial aims to help ascertain whether a combination of gum disease therapy and colchicine therapy will reduce the risk for having a cardiovascular incident. Colchicine is approved in Australia to treat acute gout. However, it is not approved to treat cardiovascular disease. Therefore, the combination of colchicine and gum disease therapy is an experimental treatment and must be tested to see if it is an effective treatment for cardiovascular disease.

The results of this research will be used by a member of the research team (Ms Lauren Church) to obtain a Doctor of Philosophy (Dentistry) degree.

This research has been initiated by the study doctors Professor Clara Chow and Professor Joerg Eberhard and is being conducted by The Western Sydney Local Health District.

3 What does participation in this research involve?

You will be participating in a randomised controlled research project. Sometimes we do not know which treatment is best for treating a condition. To find out we need to compare different treatments. We put people into groups and give each group a different treatment. The results are compared to see if one is better. To try to make sure the groups are the same, each participant is put into a group by chance (random).

This study will be conducted over a 2-month period.

If you agree to participate in this trial, you will first be screened to see if you are likely to have gum disease. The screening process involves answering 13 questions about your gum health, oral hygiene practices and oral health knowledge. If the screening process identifies that you are likely to have gum disease you will be invited to undergo an oral examination and you will be asked to provide a blood sample. The oral examination and the blood sampling will take place at the beginning of the study and at the end. You will also be asked to provide your preferred contact details for future visits and we recommend that you provide contact details for a friend or family member in case we cannot contact you.

- The oral examination will be a standard way of measuring the health of your gums using dental instruments to assess the health of your mouth.
- A blood sample from a vein equivalent to 20 millilitres (or 4 teaspoons) will be taken after the oral examination. This sample of blood will be tested for markers (indicators) of your risk for a heart attack.

If you are assigned to the treatment groups, your gum disease will be treated by a member of the research team, who is a registered oral health practitioner, based on the common Australian recommendations for comprehensive therapy of gum disease (published by the American Academy of Periodontology). The therapy will involve 3 treatment visits. Each visit will take about 1 hour, the first visit will consist of an instruction phase, where we will explain how to improve oral hygiene especially in regions that are hard to reach. We will clean your teeth in the same way you may have experienced at your dentist during regular check-ups. Two additional visits on 2 consecutive days will be required for the treatment of gum disease. During these visits we will clean the root surfaces below the gum line to remove bacterial deposits. We will use special manual and oscillating instruments using local anaesthesia and we will complete one side of your mouth at each visit. Teeth with a poor prognosis may be removed in consultation with you regarding your own preferences.

If you are assigned to a non-treatment group, your disease treatment will happen at the end of the trial.

The therapy with colchicine will start at the beginning of the study according to the recommendation of the cardiologist in charge.

In addition, the researchers would like to have access to your medical record to obtain information relevant to the study.

This research project has been designed to make sure the researchers interpret the results in a fair and appropriate way and avoids study doctors or participants jumping to conclusions.

There are no additional costs associated with participating in this research project, nor will you be paid; however, you may be reimbursed for any reasonable travel, parking and other expenses associated with the research project visit. All medication, tests and medical care required as part of the research project will be provided to you free of charge.

It is desirable that your current dentist be advised of your decision to participate in this research project. If you have a regular dentist, we strongly recommend that you inform them of your participation in this research project by providing them with the “Information for current treating dentist” letter given to you.

4 What do I have to do?

As a participant in this study you will be required to attend all dental appointments as scheduled in order to receive the gum treatment. If you are assigned to one of the groups receiving colchicine treatment you will also be required to take 1 colchicine tablet per day.

Rest assured, you will have no restrictions on your lifestyle, diet, regular medication or whether you can donate blood.

5 Other relevant information about the research project

There will be a total of 60 participants in this study, allocated to one of four arms (15 participants per arm). The project involves researchers from Westmead Hospital, the Westmead Centre for Oral Health and the Charles Perkins Centre.

6 Do I have to take part in this research project?

Participation in any research project is voluntary. If you do not wish to take part, you do not have to. If you decide to take part and later change your mind, you are free to withdraw from the project at any stage.

If you do decide to take part, you will be given this Participant Information and Consent Form to sign and you will be given a copy to keep.

Your decision whether to take part or not to take part, or to take part and then withdraw, will not affect your routine treatment, your relationship with those treating you or your relationship with Westmead Hospital of The University of Sydney.

7 What are the alternatives to participation?

You do not have to take part in this research project to receive treatment at Westmead hospital. Other options are available; these include no treatment or receiving gum treatment from a private dentist. Your study doctor will discuss these options with you before you decide whether or not to take part in this research project. You can also discuss the options with your local doctor/dentist.

8 What are the possible benefits of taking part?

We cannot guarantee or promise that you will receive any benefits from this research; however, possible benefits include treatment of gum disease which normally incurs heavy costs if treated privately or long wait periods if you are eligible for treatment in the public health care system.

9 What are the possible risks and disadvantages of taking part?

Medical treatments often cause side effects. You may have none, some or all of the effects listed below, and they may be mild, moderate or severe. If you have any of these side effects, or are worried about them, talk with your study doctor. Your study doctor will also be looking out for side effects.

There may be side effects that the researchers do not expect or do not know about and that may be serious. Tell your study doctor immediately about any new or unusual symptoms that you get.

Many side effects go away shortly after treatment ends. However, sometimes side effects can be serious, long lasting or permanent. If a severe side effect or reaction occurs, your study doctor may need to stop your treatment. Your study doctor will discuss the best way of managing any side effects with you.

This research involves gum treatment that that is identical to gum treatment you may experience during private dental appointments with a dentist or oral health therapist. All treatment follows standardised protocols. This treatment may be associated with temporary mild pain after the dental procedures and the inherited risks of local anaesthesia. Colchicine is a medication commonly used to treat gout. Nausea, vomiting, stomach pain and diarrhoea are side effects that may be associated with the intake of this medication. Please also note that since you are currently on statin therapy you may be at an increased risk of colchicine toxicity. If you experience any of the above symptoms please contact Dr Akhter immediately who will refer you to Professor Chow, or to the Westmead Hospital Emergency Department. The contact details for Dr Akhter can be found at the end of this document.

If treatment is required for any medical condition within the duration of the trial, you will be required to leave the study in order to receive the required treatment.

The effects of Colchicine on the unborn child and on the newborn baby are not known. Because of this, it is important that research project participants are not pregnant or breast-feeding and do not become pregnant during the course of the research project. You must not participate in the research if you are pregnant or trying to become pregnant, or breast-feeding. If you are female and child-bearing is a possibility, you will be required to undergo a pregnancy test prior to commencing the research project. If you are male, you should not father a child or donate sperm for at least 10 days after the last dose of study medication. Both male and female participants are strongly advised to use effective contraception during the course of the research and for a period of 10 days after completion of the research project. You should discuss methods of effective contraception with your study doctor.

If you do become pregnant whilst participating in the research project, you should advise your study doctor immediately. Your study doctor will withdraw you from the research project and advise on further medical attention should this be necessary. You must not continue in the research if you become pregnant.

You should advise your study doctor if you father a child while participating in the research project. Your study doctor will advise on medical attention for your partner should this be necessary.

Having a blood sample taken may cause some discomfort, bruising, minor infection or bleeding. If this happens, it can be easily treated.

This research project involves exposure to a very small amount of radiation from radiographs taken for dental purposes. As part of everyday living, everyone is exposed to naturally occurring background radiation and receives a dose of about 2 millisieverts (mSv) each year. The effective dose from this research project is about 0.08 mSv. At this dose level, no harmful effects of radiation have been demonstrated, as any effect is too small to measure. This risk is believed to be minimal.

10 What will happen to my test samples?

Samples of your blood obtained for the purpose of this research project will be transferred to Pathology West from Westmead Hospital for testing. Your blood samples will not be sold by The University of Sydney.

If you provide additional consent, the blood samples will be stored at the Westmead Oral Health Biobank.

11 What if new information arises during this research project?

Sometimes during the course of a research project, new information becomes available about the treatment that is being studied. If this happens, your study doctor will tell you about it and discuss with you whether you want to continue in the research project or not. If you decide to continue in the research project you will be asked to sign an updated consent form.

Also, on receiving new information, your study doctor might consider it to be in your best interests to withdraw you from the research project. If this happens, he/ she will explain the reasons and arrange for your regular health care to continue.

12 Can I have other treatments during this research project?

Whilst you are participating in this research project, you may not be able to take some or all of the medications or treatments you have been taking for your condition or for other reasons. It is important to tell your study doctor and the study staff about any treatments or medications you may be taking, including over-the-counter medications, vitamins or herbal remedies, acupuncture or other alternative treatments. You should also tell your study doctor about any changes to these during your participation in the research project. Your study doctor should also explain to you which treatments or medications need to be stopped for the time you are involved in the research project.

13 What if I withdraw from this research project?

If you decide to withdraw from the project, please notify a member of the research team before you withdraw. This notice will allow that person or the research supervisor to discuss any health risks or special requirements linked to withdrawing.

If you do withdraw your consent during the research project, the study doctor and relevant study staff will not collect additional personal information from you, although personal information already collected will be retained to ensure that the results of the research project can be measured properly and to comply with law. You should be aware that data collected by the sponsor up to the time you withdraw will form part of the research project results. If you do not want them to do this, you must tell them before you join the research project.

14 Could this research project be stopped unexpectedly?

This research project may be stopped unexpectedly for a variety of reasons. These may include reasons such as:
• Unacceptable side effects
• The drug/treatment/device being shown not to be effective
• The drug/treatment/device being shown to work and not need further testing
• Decisions made in the commercial interests of the sponsor or by local regulatory/health authorities.

15 What happens when the research project ends?

At the end of the trial, all participants will be advised to visit a private dentist for continued dental treatment. A summary of the results of the study will be sent to you in approximately March 2021.

Part 2 How is the research project being conducted?

16 What will happen to information about me?

By signing the consent form you consent to the study doctor and relevant research staff collecting and using personal information about you for the research project. Any information obtained in connection with this research project that can identify you will remain confidential. The information will only be accessible to the study investigators and will be kept in a locked filing cabinet at the Westmead Applied Research Centre. A source document will be generated that links the identifiable information to the study code and this will be held separately and securely on a password protected PC also at the Westmead Applied Research Centre. Your information will only be used for the purpose of this research project and it will only be disclosed with your permission, except as required by law.

It is anticipated that the results of this research project will be published and/or presented in a variety of forums. In any publication and/or presentation, information will be provided in such a way that you cannot be identified.

In accordance with relevant Australian privacy and other relevant laws, you have the right to request access to your information collected and stored by the research team. You also have the right to request that any information with which you disagree be corrected. Please contact Dr Akhter (details at the end of this document) if you would like to access your information.

Any information obtained for the purpose of this research project and for the future research described in Section 16 that can identify you will be treated as confidential and securely stored. It will be disclosed only with your permission, or as required by law.

17 Complaints and compensation

If you suffer any injuries or complications as a result of this research project, you should contact the study team as soon as possible and you will be assisted with arranging appropriate medical treatment. If you are eligible for Medicare, you can receive any medical treatment required to treat the injury or complication, free of charge, as a public patient in any Australian public hospital.

18 Who is organising and funding the research?

This research project is a collaborative research project between ProfessorClara Chow and Dr Rahena Akhtar from the Western Sydney Local Health District, and Professor Joerg Eberhard from the University of Sydney.

19 Who has reviewed the research project?

All research in Australia involving humans is reviewed by an independent group of people called a Human Research Ethics Committee (HREC). The ethical aspects of this research project have been approved by the HREC of the Western Sydney Local Health District.

This project will be carried out according to the *National Statement on Ethical Conduct in Human Research (2007)*. This statement has been developed to protect the interests of people who agree to participate in human research studies.

20 Further information and who to contact

The person you may need to contact will depend on the nature of your query.

If you want any further information concerning this project or if you have any medical problems which may be related to your involvement in the project (for example, any side effects), you can contact the principal study doctor, Dr Akhter, or any of the following people:

Clinical contact person

Name	Dr Rahena Akhter
Position	Principal Investigator
Telephone	0402 933 527
Email	rahena.akhter@sydney.edu.au

For matters relating to research at the site at which you are participating, the details of the local site complaints person are:

Complaints contact person

Position	Patient Experience Unit
Telephone	8890 7014
Email	Wslhd-westmead-feedback@health.nsw.gov.au

If you have any complaints about any aspect of the project, the way it is being conducted or any questions about being a research participant in general, then you may contact:

Reviewing HREC approving this research and HREC Executive Officer details

Reviewing HREC name	*WSLHD HREC Committee*
HREC Executive Officer	*Kellie Hansen*
Telephone	*8890 9007*
Email	*Wslhd-researchoffice@health.nsw.gov.au*

HREC Office contact (Single Site -Research Governance Officer)

WMD Research Office	WSLHD Research Governance Office
Telephone	02 8890 9007
Email	Wslhd-researchoffice@health.nsw.gov.au

Consent Form - *Adult providing own consent*

Title	Reducing the systemic inflammation associated with periodontitis to reduce risk in patients with coronary artery disease and on statin therapy- a randomised feasibility study
Short Title	Periodontitis and coronary artery disease
Protocol Number	2019/PID00206
Project Sponsor	WSLHD
Coordinating Principal Investigator	Professor Clara Chow
Principal Investigator	Dr Rahena Akhter
Associate Investigator(s)	Professor Joerg Eberhard
Location	Westmead Hospital

Declaration by Participant

I have read the Participant Information Sheet or someone has read it to me in a language that I understand.

I understand the purposes, procedures and risks of the research described in the project.

I give permission for my doctors, other health professionals, hospitals or laboratories outside this hospital to release information to The University of Sydney concerning my disease and treatment for the purposes of this project. I understand that such information will remain confidential.

I acknowledge that pharmaceutical companies and any regulatory authorities may have access to my medical records **specifically related** to this project to monitor the research in which I am agreeing to participate. However, I understand my identity will not be disclosed to anyone else or in publications or presentations.

I have had an opportunity to ask questions and I am satisfied with the answers I have received.

I freely agree to participate in this research project as described and understand that I am free to withdraw at any time during the study without affecting my future health care.

I understand that I will be given a signed copy of this document to keep.

Name of Participant (please print) _____

Signature _____ Date _____

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the research project, its procedures and risks and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of, and information concerning, the research project.

Note: All parties signing the consent section must date their own signature.

I consent to the storage and use of blood samples taken from me for use, as described in the relevant section of the Participant Information Sheet, for:

- This specific research project
- Other research that is closely related to this research project
- Any future research.

Name of Participant (please print) _____

Signature _____ Date _____

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning the research project.

Note: All parties signing the consent section must date their own signature.

Form for Withdrawal of Participation - *Adult providing own consent*

Title	Reducing the systemic inflammation associated with periodontitis to reduce risk in patients with coronary artery disease and on statin therapy- a randomised feasibility study
Short Title	Periodontitis and coronary artery disease
Protocol Number	2019/PID00206
Project Sponsor	WSLHD
Coordinating Principal Investigator	Professor Clara Chow
Principal Investigator	Dr Rahena Akhter
Associate Investigator(s)	Professor Joerg Eberhard
Location	Westmead Hospital

Declaration by Participant

I wish to withdraw from participation in the above research project and understand that such withdrawal will not affect my routine treatment, my relationship with those treating me or my relationship with Westmead Hospital or The University of Sydney.

Name of Participant (please print) _____

Signature _____ Date _____

In the event that the participant's decision to withdraw is communicated verbally, the Study Doctor/Senior Researcher will need to provide a description of the circumstances below.

Declaration by Study Doctor/Senior Researcher†

I have given a verbal explanation of the implications of withdrawal from the research project and I believe that the participant has understood that explanation.

Name of Study Doctor/
Senior Researcher† (please print) _____

Signature _____ Date _____

† A senior member of the research team must provide the explanation of and information concerning withdrawal from the research project.

Note: All parties signing the consent section must date their own signature.

WHO data registry

Data Category	**Information**
Primary registry and trial identifying number	Australia New Zealand Clinical Trials Registry ACTRN12619001573145p
Date of registration in primary registry	14/11/2019
Secondary identifying numbers	U1111-1267-9602 (UTN) 2019/ETH00200
Source(s) of monetary or material support	The University of Sydney
Primary sponsor	The Western Sydney Local Health District
Secondary sponsor(s)	N/A
Contact for public queries	Dr Rahena Akhter
Contact for scientific queries	Prof Joerg Eberhard
Public title	Treatment of gum disease to reduce cardiovascular risk
Scientific title	Targeting the systemic inflammation associated with periodontitis to reduce risk in patients with coronary artery disease and on statin therapy- a randomized feasibility study
Countries of recruitment	Australia
Health condition(s) or problem(s) studied	Coronary artery disease Periodontitis
Intervention(s)	Participants will be allocated to one of 4 arms: 1) Periodontal treatment 2) Colchicine administration 3) Periodontal treatment + colchicine administration 4) No treatment Periodontal treatment will involve scaling and root planing. This will be performed over 3 separate appointments, beginning at baseline with a 1-2 week interval between appointments. Treatment will be carried out by a registered oral health practitioner at the Westmead Centre for Oral Health. Colchicine will be administered via 0.5mg tablets to be taken by the participants once daily for 8 weeks.
Key inclusion and exclusion criteria	**Medical inclusion criteria:** Have coronary artery disease (acute coronary syndrome/ stable angina and are on statin therapy. ≥ 18 years. **Medical Exclusion criteria:** currently taking or have had antibiotic therapy in the last 3 months. currently pregnant, lactating of planning pregnancy. severe renal impairment: GFR <30. severe hepatic impairment: History of CKD and or alanine aminotransferase >3 upper limit of normal [ULN]). Blood dyscrasias. Taking medications that interact with Colchicine. **Dental inclusion criteria:**

	No subgingival scaling and root planning in the last 6 months. ≥ 15 teeth. Mod-severe periodontitis. **Dental Exclusion criteria:** Received subgingival scaling and root planning in the last 6 months. < 15 teeth Mild periodontitis
Study type	Interventional
Date of first enrolment	23/06/2022
Target sample size	60
Recruitment status	Recruiting
Primary outcome(s)	1) Difference in hsCRP
Key secondary outcomes	1) Difference in lipids and periodontal parameters 2) Feasibility measures (recruitment conversion rate, completion rate, safety and tolerability, trial evaluation)