Participant Information Sheet

The PUMAS Study:
Reducing the Workload of the Heart in Aortic Stenosis

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Study Contact Details:	Dr Peter McLeod via Dunedin Public Hospital switchboard 03 4740999	Email: *pumas@southerndhb.govt.nz*

You are invited to take part in this study because you have been diagnosed with narrowing of the aortic valve, called aortic stenosis (AS). This was seen on an ultrasound of your heart (echocardiogram) and has been classified as mild to moderately narrowed. At the moment, this is unlikely to be severe enough to be causing much extra pressure on the heart muscle. We are writing to invite you to take part in this study, which looks at whether commonly used blood pressure medications can reduce the workload on the heart, with the aim of reducing or slowing the development of heart problems associated with this condition and, in particular, protect the heart muscle.

This Participant Information Sheet will help you decide if you'd like to take part. It sets out why we are doing the study, what your participation would involve, what the benefits and risks to you might be, and what would happen after the study ends. We will go through this information with you and answer any questions you may have. You do not have to decide today whether or not you will participate in this study. Before you decide, we encourage you to talk about the study with other people, such as family, whānau, friends, or healthcare providers.

If you agree to take part in this study, you will be asked to sign the Consent Form on the last page of this document. You will be given a copy of both the Participant Information Sheet and the Consent Form to keep. This document is 12 pages long, including the Consent Form. Please make sure you have read and understood all the pages.

WHAT IS THE PURPOSE OF THE STUDY?

The aortic valve is one of four flexible valves in the heart. Aortic stenosis (AS) is a disease of the aortic valve and is caused by a progressive build-up of calcium in the valve itself. Over time the aortic valve gets stiffer, which leads to an increase in the pressure inside the heart causing the heart to work harder. This increased workload leads to potentially irreversible scarring of the heart muscle, reducing the ability of the heart to function.

Currently there are no medications available to slow the progression of AS and treatment is based on careful observation until aortic valve replacement (AVR), which is an expensive and sometimes risky procedure. AVR is typically only considered when individuals present with problems or if the heart muscle begins to fail. Even after AVR, scar tissue remains in the heart

and can increase the risk of ongoing heart related issues such as heart failure and death. It is unknown whether reducing the workload of the heart due to aortic stenosis can alter this process, protect the heart muscle and possibly improve health outcomes related to AS.

This study aims to initially recruit 200 participants to analyse the effectiveness of commonly prescribed medications on reducing the workload on the heart, starting when aortic stenosis in a mild to moderate stage. Participants will be randomised equally to either 'standard care', which is current routine clinical care, or the 'medicines group', which involves targeted medical therapy. Standard care means being followed-up by your primary care practitioner, in conjunction with the cardiology department, usually having repeat heart scans every one to five years. There are no treatments to date that have been shown to slow the progression of AS. The medicines group uses a combination of three readily available medications which are routinely used in clinical practice; a calcium channel blocker, **amlodipine**; an angiotensin receptor blocker **candesartan**; and the beta blocker, **bisoprolol**. These have specific mechanisms that may protect the heart muscle in aortic stenosis.

The time it takes for AS to progress varies, in some individuals it can take a few years for heart problems to develop, and in other individuals it can take decades. That is why in our study we plan to have an initial two year period of direct contact with you and then we plan to monitor you from a distance in the longer term (at least 10 years).

The investigations and procedures involved in this study are planned according to the best available medical knowledge and standards and have been reviewed by the Health and Disability Ethics Committee (reference 21/NTA/164). The lead investigator is Dr Sean Coffey; Senior Lecturer, Dunedin School of Medicine, University of Otago; Consultant Cardiologist, Cardiology Department, Southern District Health Board. The study is funded by grants from the University of Otago, Dunedin, New Zealand, the Healthcare Otago Charitable Trust, Dunedin, New Zealand, the Health Research Council of New Zealand and the Health Lottery New Zealand.

WHO CAN TAKE PART IN THE STUDY?

You have been invited to participate in this study because you have had an ultrasound of your heart (echocardiogram) which has identified that you have mild or moderate aortic stenosis. We are inviting individuals between the ages of 18 to 90 years, without other major medical problems, to take part. You may be able to take part even if you normally take one or more of the medicines in this study.

WHAT WILL MY PARTICIPATION IN THE STUDY INVOLVE?

Your participation involves one visit at the hospital and your choice of further visits either at the hospital, over the phone or online, as well as your agreement to possibly take medicines as part of the study and measure your own blood pressure.

At the start of the study

The first visit will take place at the hospital and will take around 60 minutes, this is what we call our baseline visit. We will ask you for more detail about yourself and your health history, complete this form recording your informed consent, and arrange a blood test to measure biomarkers of your health, such as your kidney function. No blood samples will be stored. We will ask you to fill in some questionnaires about your health and how you are feeling. We will also give you a home blood pressure monitor, record your blood pressure, and allocate you to a treatment group at random.

Randomisation

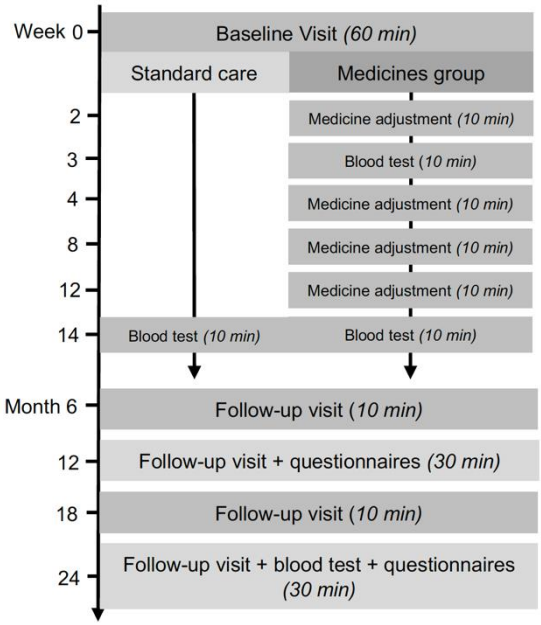
You have an equal chance to be randomised to one of the two study groups. The standard care group continues with medical care as usual. What this means is that your GP, or other healthcare provider, will manage your healthcare as usual without any further input from the research team other than observation study visits in the first two years, and data linkage afterwards (see below). The medicines group will be assigned a combination of bisoprolol, candesartan, and amlodipine. We will manage the dose increase of these medications with you.

Medicines adjustment

If you are in the medicines group, we will provide you with step wise instructions about how to start taking the medications, and provide you with a prescription for these. You will start at low doses and will have a schedule to slowly increase the amount every week or fortnight, until you reach the maximum dose that suits you. These medications are very commonly used together and generally well tolerated. The time to reach the maximum dose may take a few months. During this time we will make contact with you around every 2-4 weeks, depending on your specific experience with the medications, to ask you whether you are experiencing any issues with these medications. A blood test to check your kidney and salt levels will be done after 3 weeks and again once you have reached your maximum dose, usually around 12 weeks. When you have reached your maximum dose we will send a letter to your GP asking them to maintain you at this for the duration of the trial period (approximately 10 years) or until your GP or another healthcare provider believes you no longer receive benefit from the medicines.

Follow-up

For the rest of the study, we can do visits either in person, over the telephone or online, via a platform like Zoom – the choice will be up to you. For the first few months while your treatment is being adjusted to suit you, most of the study visits will take around 10 minutes, with slightly longer ones (30 mins) at the one and two year mark. If you are in the standard care part of the study, there is a single additional blood test at 12 weeks, to check your kidney and salt levels again. No contact with the research team directly is planned after two years, although you are likely to still be undergoing follow-up with your own doctor or your usual cardiologist. For most of the study visits, we will ask you to measure your own blood pressure at home for a few days beforehand – we will give you a blood pressure machine (that will be yours to keep) to do this. At the one and two year marks, we will also ask you to fill in the same questionnaires you filled in at the start. At the 24 month study visit we will ask you to repeat the same blood tests we did at the baseline visit.



The figure summarises the proposed study visits and the expected time that each visit may take. Study participants will be asked to record their blood pressure in the lead up to a study visit. We expect that it should take around 5 minutes to perform this each time.

Long term follow-up

We don't have any planned study visits after two years. Instead, we ask your permission to access and store your electronic health information including your heart scans for analysis of factors related to your heart function and measures of your aortic stenosis.

With your permission, we will ask for information from the Ministry of Health's national data collections, including hospital admissions and hospital procedures. This will allow us to look for events related to your heart, as well as medicines you may have been prescribed. We will look at the Accident Compensation Corporation (ACC) database for injuries that may be related to your heart valve disease or the study medications, such as injuries from falls due to low blood pressure. This will help us determine whether the treatments are effective and safe in the long term.

Sometimes we lose contact with people in a study. Because of this we will ask you for the details of someone we can make contact with if we find ourselves in the situation that we cannot find you or for some reason you are unwell or unable to speak to the study team.

Participation in the study will not affect any routine clinical care for your aortic stenosis. As such you may have further imaging of your heart (for example an echocardiogram) to assess progression of the disease and the function of your heart as part of your standard care. We ask for permission to access your future and any previous cardiac imaging you may have had to determine the rate progression of your aortic stenosis and to see if there are any differences between the groups.

VOLUNTARY PARTICIPATION AND WITHDRAWAL FROM THIS STUDY

Your participation in our study is entirely voluntary (your choice). You may have a friend, family or whānau support to help you understand the risks and/or benefits of this study and any other explanation you may require. You do not have to take part in this study, and if you choose not to take part, this will not affect any future care or treatment. If you do agree to take part you are free to withdraw from the study at any time, without having to give a reason. This will in no way affect your future or continuing health care. If you wish to withdraw from the study please

contact the research team via phone (Dr Peter McLeod via Dunedin Public Hospital switchboard 03 4740999), or, preferably, email (pumas@southerndhb.govt.nz).

WHAT ARE THE POSSIBLE RISKS AND BENEFITS OF THIS STUDY?

We do not foresee any large or unexpected risks from participating in this study. We are using routinely prescribed medicines, and using a standard method to increase the dose of the medicines. We will use fully trained staff to undertake the testing in a standardised manner. The risk of side effects due to the medications is small and we will manage these risks during the study by regularly monitoring your health record and through our study visits with you. If necessary, we can reduce the dose or even stop any of the medicines. Many thousands of people worldwide are taking all of these medicines on a long term basis without any problems, often in the same combination and doses in this study.

The most common side effects reported for individuals taking amlodipine are; headache, sleepiness, dizziness, heart palpitations, flushing, abdominal pain, nausea, oedema (swelling) and fatigue. Less common side effects include leukopenia (a decrease in the number of white blood cells), thrombocytopenia (a decrease in the number of platelets), hyperglycaemia, insomnia, mood changes, nervous system disorders (including peripheral neuropathy, taste perversion, syncope (fainting), tremor, visual disturbances, tinnitus (ringing in the ears), hypotension (low blood pressure), cough, altered bowel habits, dry mouth, muscle cramps and/or pain, increased urinary frequency, nocturia, gynecomastia, impotence, malaise, weight increase/decrease. Rarely allergic reactions have been reported, including itching and rash. Very rare side effects include hepatitis, jaundice and liver enzyme level increase.

The most common side effects reported for individuals taking candesartan are; hypotension, hyperkalaemia (high potassium level in blood), and kidney impairment. Very rare side effects include low levels of certain blood cells, hyponatraemia (low levels of sodium), dizziness, cough, increased liver enzymes, abnormal liver function or hepatitis, angioedema (swelling), rash, urticaria (hives), pruritus (itchy skin), back pain and kidney impairment.

The most common side effects reported for individuals taking bisoprolol are; bradycardia (slow heart beat), dizziness, headache, constipation, diarrhoea, nausea, vomiting, cold extremities, hypotension and fatigue. Less common side effects include bronchospasm (in individuals with a history of bronchial asthma or history of obstructive airways), muscle weakness and cramps, orthostatic hypotension, sleep orders and depression. Rare to very rare side effects include increased liver enzymes, syncope, hepatitis, conjunctivitis, allergic rhinitis, hearing impairment, impotence, itching, flushes, rash, alopecia, hepatitis, nightmares and hallucinations.

Although a large number of possible side effects for each medication has been listed, apart from low blood pressure, taking a number of these medicines together does not increase the risk of these side effects. **It is also important to note that, in large clinical trials, medicines rarely have to be stopped due to side effects and typically the rate of stopping due to side effects is similar to that seen with placebo (no active medicine).**

In our study we are asking you to measure and record your blood pressure at home using a blood pressure monitor. Some individuals may feel anxious if they have an unexpectedly high or low blood pressure reading. We'll be available to advise you if you have any concerns.

Your arm may be slightly sensitive after the blood tests, and/or you may experience some minor bruising, however this quickly fades.

There are no guaranteed benefits to taking part in this study. All study participants in this study are making a contribution to research in aortic stenosis which has the potential to improve health outcomes in the future. Like people taking part in any clinical trial, compared to people not taking part in a trial there may be benefits such as lower rates of heart problems, purely due to the closer monitoring.

WHAT ARE THE ALTERNATIVES TO TAKING PART?

There are currently no therapies available to slow the progression of aortic stenosis. If you choose not to participate in this study you will continue with standard management of AS under the care of your general practitioner, in combination with the cardiology department, which usually involves scans in the future to see how it is progressing.

WILL ANY COSTS BE REIMBURSED?

You will not have to pay to take part in the study. You will receive a $50 New World voucher for participating in this study which will be given to you at the baseline study visit. Study participants will be allocated a home blood pressure monitor at the baseline study visit, and this is yours to keep. You will not receive remuneration for any future revenue generated directly or indirectly from the results of this study.

WHAT WILL HAPPEN TO MY INFORMATION?

During this study the members of the research team will record information about you and your study participation. This includes, but is not limited to, the results of any study assessments, and information from your hospital and general practitioner records where available. You also have the right to request that personal information collected about you is corrected. You cannot take part in this study if you do not consent to the collection of this information.

Identifiable Information

Identifiable information is any data that could identify you (e.g. your name, date of birth, or address). The following groups may have access to your identifiable information:

- Specific members of the research team (to complete study assessments or in cases where a significantly abnormal test result was returned requiring clinical follow up by your appropriate healthcare provider.)

- The ACC and/or the University of Otago and their representatives, if you make a compensation claim for study-related injury. Identifiable information is required in order to assess your claim.

- The sponsor, ethics committees, or government agencies from New Zealand or overseas, if the study or site is audited. Audits are done to make sure that participants are protected, the study is run properly, and the data collected is correct.

We will notify your general practitioner of your enrolment in the PUMAS study and the medication dose you are on when you have achieved your maximum tolerable dose. In addition an alert will be placed in your electronic health record within the Southern District Health Board system stating that you have enrolled in the study.

De-identified (Coded) Information

To make sure your personal information is kept confidential, information that identifies you will not be included in any report generated during the study. Instead, you will be identified by a unique study code which will be assigned to you on study enrolment. The study team will keep a list linking your code with your name, so that you can be identified by your coded data if needed (please see above).

Access to your coded information will include, but is not limited to the following groups:

- Trained members of the research team to conduct the study and to perform data analysis.

- Other researchers for re-analysis and peer review of study data.

- Regulatory or other governmental agencies.

The results of the study may be published or presented, but not in a form that would reasonably be expected to identify you. As this is a clinical trial, de-identified data, will be made available on public servers after the end of the trial to allow other researchers to re-analyse the trial to check the findings, and to do other analyses of the data. Your de-identified data may be added to other datasets for the future study of aortic stenosis.

Anonymised Information

The research team may remove the code from your de-identified information – this is called 'anonymisation'. This makes it very difficult (but not impossible) to identify the information that belongs to you. We also ask to contribute your anonymised information to a database which will be available to the public for research, education and teaching purposes – this is an **optional** part of the study. This anonymised information includes images of your heart and some clinical information, such as; age, gender, height, weight, blood pressure, smoking, alcohol, ethnicity and medical conditions (for example diabetes). Anonymised information means all personal details, such as your name or anything that might directly identify you, will be removed. If you agree, this anonymised data will be placed on publicly accessible websites in the future. Our aim is that other researchers and teachers will use to improve human health.

Data-Linking

In this study we will be linking your study information with other data sets which include information about you. This is called 'data-linking'. Data-linking in this study is mandatory so we can see if the treatment works, without you having to come in for study visits. We plan to follow you for a minimum of 10 years using data-linking, even if you have a heart valve procedure performed.

In this study we will link with the Ministry of Health's (MoH) national health data collections and the ACC data collection using your National Health Identifier (NHI). We are linking to the MoH dataset to monitor for medical events, including but not limited to, attending the hospital for health related events or undergo hospital procedures such as aortic valve replacement. We will use this information to monitor study outcomes related to your aortic stenosis, as well as benefits and possible risks related to the study intervention. We can also use this to tell what medications have been given to you, which will help us see if there have been any changes to this. We will link with ACC systems to monitor for any falls or injuries you might have had, either related to your aortic stenosis or the study medicines.

Future Research Using Your Information

Your coded (de-identified) information may be used for future research related to both aortic stenosis and other medical and/or scientific research that is unrelated to the current study.

If you agree to your anonymised information being made publicly available, this can be used for any research, education, or teaching purposes, including commercial.

In both cases, the data may be held overseas, and future research may be conducted overseas. You will not be told when future research is undertaken using this information. Your information may be shared widely with other researchers and you will not get reports or other information about any future research that is done using your information. Your information may be used indefinitely for future research. Once your information has been made available for future research, it will not be possible to withdraw it from use.

Security and Storage of Your Information

Your identifiable information will be stored in a secure database hosted on the secure University of Otago servers during the study. Any paper documents generated will be kept in lockable rooms within the Dunedin Public Hospital premises. Your data will be stored securely for at least 10 years after completion of the study, then destroyed. All storage will comply with local and/or international data security guidelines. Destruction of any data (paper or digital) will be performed in a secure manner following University of Otago disposal policies to protect your privacy and confidentiality. De-identified and anonymous data will be indefinitely available.

Risks

Although efforts will be made to protect your privacy, absolute confidentiality of your information cannot be guaranteed. Even with coded and anonymised information, there is no guarantee that you cannot be identified. The risk of people accessing and misusing your information (e.g. making it harder for you to get or keep a job or health insurance) is currently very small, but may increase in the future as people find new ways of tracing information.

Rights to Access Your Information

You have the right to request access to your information held by the research team. You also have the right to request that any information you disagree with is corrected. We will tell you of any findings that we have that may impact on your health. If you have any questions about the collection and use of information about you, you should ask a member of the research team.

Rights to Withdraw Your Information

You may withdraw your consent for the collection and use of your information at any time, by informing a member of the research team. You may choose to partly withdraw from the study, or fully withdraw from the study.

If you choose to partly withdraw from the study you will end your direct contact with us, but we will continue to monitor your aortic stenosis via your health record and linking to other databases (please see section "What will happen to my information" for more detail about data-linking).

If you want to fully withdraw from the study, we will stop collecting data about you. We will keep a record of your age, gender, ethnicity and decision to withdraw from the study. We keep this data so that we can identify any patterns to withdrawals from the study. This is to protect the quality of the study and to ensure we do not inadvertently contact you again for possible enrolment.

You will not be able to withdraw your de-identified data if we have shared it with other researchers. If your code is removed from your information, making it anonymised, you will not be able to access, correct or withdraw your information, even if you change your mind about it being used (as we will not be able to identify your data specifically).

WHAT IF SOMETHING GOES WRONG?

If you were injured in this study due to the intervention, you would be **eligible to apply** for compensation from ACC just as you would be if you were injured in an accident at work or at home. This does not mean that your claim will automatically be accepted. You will have to lodge a claim with ACC, which may take some time to assess. If your claim is accepted, you will receive funding to assist in your recovery.

In the unlikely event that ACC determines that their cover did not apply to your injury, then the University of Otago's clinical trial insurance would apply. This cover would provide you with compensation equivalent to that you would otherwise have been entitled to under the Accident Compensation Act 2001. By signing the Consent Form for this study, should ACC decline cover, you are explicitly agreeing that compensation for any injury will be as per the terms of University's then current clinical trials insurance cover, the full terms and conditions of which are freely available on request.

If you have private health or life insurance, you may wish to check with your insurer that taking part in this study won't affect your cover.

WHAT HAPPENS AFTER THE STUDY?

Data will be coded, stored and protected for a minimum of 10 years after the completion of the study.

We expect that the final results of this study will be published in peer reviewed medical journals. There may be some time between the conclusion of data collection and publication of results. You will not be personally identified in any presentations or publications from the study. If you wish, we can provide you with a written summary of the findings of our study.

WHO DO I CONTACT FOR MORE INFORMATION OR IF I HAVE CONCERNS?

If you have any questions, concerns or complaints about the study at any stage, you can contact:

Lead investigator:	Dr Sean Coffey
Study contact:	Dr Peter McLeod via Dunedin Public Hospital switchboard (03) 4740999
Study email:	pumas@southerndhb.govt.nz

If you want to talk to someone who isn't involved with the study, you can contact an independent health and disability advocate on:

Phone:	0800 555 050
Fax:	0800 2 SUPPORT (0800 2787 7678)
Email:	advocacy@advocacy.org.nz

To ensure ongoing cultural safety, the Southern District Health Board encourage those who identify as Māori, and who are participating in health research or clinical trials, to seek cultural support and advice from their own Kaumātua or Kuia in the first instance, or please contact:

Wendi Raumati & Eleanor Russell Kaiāwhina Te Ara Hauora - Māori Health Unit Dunedin Hospital Phone: (03) 474 0999 ext 58649	Andrea Jerry Kaiāwhina Te Huinga Tahi Māori Health Cultural Support Southland Hospital Phone: (03) 218 1949 ext 48509

You can also contact the health and disability ethics committee (HDEC) that approved this study by phoning: **0800 4 ETHICS** or by email: **hdecs@moh.govt.nz**

Consent Form

The PUMAS Study:
Reducing the Workload of the Heart in Aortic Stenosis

I consent to the following:

I have been given sufficient time to consider whether or not to participate in this study.
I have had the opportunity to use a legal representative, whanau/ family support or a friend to help me ask questions and understand the study.
I am satisfied with the answers I have been given regarding the study and I have a copy of this consent form and information sheet.
I understand that taking part in this study is voluntary (my choice) and that I may withdraw from the study at any time without this affecting my medical care.
I consent to the research staff collecting and processing my information, including information about my health.
I consent to de-identified information from this study being placed on public databases for re-analysis and secondary analysis of the trial, and to study other questions in health and disease.
I agree to an approved auditor appointed by the New Zealand Health and Disability Ethics Committees, or any relevant regulatory authority or their approved representative reviewing my relevant medical records for the sole purpose of checking the accuracy of the information recorded for the study.
I understand that my participation in this study is confidential and that no material, which could identify me personally, will be used in any reports on this study.
I have read the 'What if Something Goes Wrong' section in the Participant Information Sheet. I agree that in the unlikely event that ACC declines cover for any injury to me arising from this study, the compensation available will be as per the terms of University's then current clinical trials insurance cover.
I know who to contact if I have any questions about the study in general.
I understand my responsibilities as a study participant.
I consent to my GP or current provider being informed about my participation in the study and of any significant abnormal results obtained during the study.
I consent to the research staff collecting, storing, and using my information, including information about my health, electronic health records, and medical images (scans) now and in the future, and understand it will only be used for further investigation into health and disease.
I consent to data-linking being performed to gather information on study outcomes and safety monitoring.
Yes I confirm the statements listed above ☐

Optional Points:

You can still take part in the study if you answer "No" to the following:

If I decide to withdraw from the study, I agree that the information collected about me up to the point when I withdraw may continue to be processed.	Yes ☐	No ☐
I agree to my anonymised data (with all personal details removed) being included on publicly accessible websites to facilitate research, teaching and education	Yes ☐	No ☐
I wish to receive a summary of the results from the study.	Yes ☐	No ☐
I wish to be contacted about future research.	Yes ☐	No ☐

Declaration by participant:
I hereby consent to take part in this study.

Participant's name: _____

Signature: _____ Date: _____

Declaration by member of research team:

I have given a verbal explanation of the research project to the participant, and have answered the participant's questions about it.

I believe that the participant understands the study and has given informed consent to participate.

Researcher's name: _____

Signature: _____ Date: _____