Strategies for Promoting Physical Activity in Clinical Care: An Evaluation of Arterial Health Impact and Physical Activity Behaviour

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ABSTRACT

With an increasing prevalence of cardiometabolic chronic diseases, there is a pressing need for effective and realistic strategies to help physicians support and engage their patients to achieve the health benefits of higher physical activity levels. Improved metrics for evaluating cardiovascular health in individuals with well-controlled risk factors are also needed, whether to examine the impact of an exercise program or to assess cardiovascular disease risk in a clinical setting. The *overall aim* of this thesis was to evaluate the effectiveness of physical activity interventions integrated into clinical care, with a focus on the arterial health impact and physical activity behavior.

The SMARTER randomized controlled trial demonstrated that a step count prescription strategy delivered by the treating physician has measurable effects on daily steps and metabolic health among adults with type 2 diabetes mellitus (T2DM) and hypertension. The work herein aimed to delineate factors that contributed to the effectiveness of the strategy and identify modifications for future implementation. Our qualitative analysis demonstrated that the strategy was feasibly integrated into clinical practice and successful in engaging most patients; however, additional support from other members of the health care team for maximal engagement and sustained use (*Manuscript 1*). Through group-based trajectory analysis we identified distinct step count patterns over time in response to the intervention (*Manuscript 2*). The trajectories were stratified as a function of initial step count levels, but the overall increase in steps/day was not restricted to either the more active or less active groups. T2DM and older age were associated with lower baseline values but were not indicators of likelihood of step count increases.

Through a pilot randomized controlled trial, we demonstrated that an intradialytic pedaling exercise is a safe and effective modality for engaging individuals with chronic kidney disease in regular physical activity (*Manuscript 3*). Importantly, 4-months of pedaling exercise led to reductions in carotid-femoral pulse wave velocity (cfPWV), the gold-standard measure of arterial stiffness. The improvements were partially reversed 4 months after exercise discontinuation, emphasizing the need for maintenance of regular physical activity in this population.

Individuals with T2DM are known to have an exaggerated blood pressure response to maximal exercise. The 'arterial stress test' which consists of measurements of arterial stiffness before and immediately after acute maximal exercise provided a useful model for examining the ability of the arteries to respond to increased demands. Our findings revealed that individuals with T2DM exhibit an altered arterial stiffness response to acute maximal exercise compared to individuals without T2DM, independently of resting arterial stiffness and the blood pressure post-exercise (*Manuscript 4*).

Finally, we evaluated methodological considerations for the measurement of arterial stiffness and physical activity. We observed differences in ActiGraph-derived physical activity measures between waist and wrist accelerometer locations, but also important differences in their relationship with arterial stiffness; waist location accelerometer-derived physical activity signaled a relationship with cfPWV, but the wrist location did not (*Manuscript 5*). We also compared different approaches that have been adopted in the literature for assessing arterial stiffness using applanation tonometry and revealed clinically meaningful differences in the reported arterial stiffness value between methods (*Manuscript 6*).

Taken together, these novel contributions will a) guide future research evaluating physical activity and cardiovascular health using modern methods such as accelerometry

and applanation tonometry, and b) facilitate building refined and sustainable physical activity strategies to address the high levels of inactivity and elevated cardiovascular risk in individuals with hypertension, T2DM and CKD.

RÉSUMÉ

Avec une prévalence croissante des maladies chroniques cardiométaboliques, il existe un besoin urgent de stratégies efficaces et réalistes pour aider les médecins à soutenir et impliquer leurs patients pour obtenir les avantages pour la santé de niveaux d'activité physique plus élevés. Des paramètres améliorés pour évaluer la santé cardiovasculaire chez les personnes ayant des facteurs de risque bien contrôlés sont également nécessaires, que ce soit pour examiner l'impact d'un programme d'exercice ou pour évaluer le risque de maladie cardiovasculaire en soins cliniques. *L'objectif général* de cette thèse était d'évaluer l'efficacité des interventions d'activité physique intégrées aux soins cliniques, en mettant l'accent sur l'impact sur la santé artérielle et le comportement lié à l'activité physique.

L'essai contrôlé randomisé SMARTER a montré qu'une stratégie de prescription de pas quotidiens fournie par le médecin traitant a des effets mesurables sur les pas quotidiens et la santé métabolique chez les adultes atteints de diabète de type 2 (DT2) et d'hypertension. Le travail ici visait à délimiter les facteurs qui ont contribué à l'efficacité de la stratégie et à identifier les modifications pour une mise en œuvre future. Notre analyse qualitative a montré que la stratégie était réalisable dans la pratique clinique et avait réussi à mobiliser la plupart des patients ; cependant, un soutien supplémentaire d'autres membres de l'équipe de soins de santé pourrait être nécessaire à un engagement maximal et une utilisation durable (*Manuscrit 1*). Grâce à l'analyse de trajectoire basée sur le groupe, nous avons identifié des modèles de comptage de pas distincts au fil du temps en réponse à l'intervention (*Manuscrit 2*). Les trajectoires ont été stratifiées en fonction des niveaux de comptage initiaux, mais l'augmentation globale du nombre de pas par jour n'était pas limitée aux groupes les plus actifs ou les moins actifs. Le T2DM et l'âge avancé

étaient associés à des valeurs de base plus faibles, mais n'étaient pas des indicateurs de la probabilité d'une augmentation du nombre de pas.

Grâce à un essai pilote contrôlé randomisé, nous avons montré qu'un exercice de pédalage intradialytique est une modalité sûre et efficace pour engager des personnes atteintes d'une maladie rénale chronique dans une activité physique régulière (*Manuscrit 3*). Il est important de noter que quatre mois d'exercice de pédalage ont entraîné une réduction de la vitesse de propagation de l'onde de pouls carotido-fémorale (VPOPcf), l'étalon d'or de la mesure de la rigidité artérielle. Les améliorations ont été partiellement inversées quatre mois après l'arrêt de l'exercice, soulignant la nécessité de maintenir une activité physique régulière dans cette population.

Les personnes atteintes de DT2 sont connues pour avoir une réponse exagérée de la pression artérielle à un exercice maximal. Le 'test de stress artériel' impliquant des mesures de rigidité artérielle au repos et à plusieurs moments après un test à l'effort jusqu'à épuisement a fourni un modèle utile pour examiner la capacité des artères à répondre à des demandes accrues. Nos résultats ont révélé que les individus atteints de DT2 présentent une réponse de rigidité artérielle altérée à l'exercice maximal aigu par rapport aux individus sans DT2, indépendamment de la rigidité artérielle au repos et de la pression artérielle après l'exercice (*Manuscrit 4*).

Enfin, nous avons évalué les considérations méthodologiques pour la mesure de la rigidité artérielle et de l'activité physique. Nous avons montré des différences dans les mesures d'activité physique dérivées d'ActiGraph entre les emplacements de l'accéléromètre à la taille et au poignet, mais également des différences importantes dans leur relation avec la rigidité artérielle ; l'activité physique dérivée de l'accéléromètre à la taille a signalé une relation avec la VPOPcf, mais pas la position au poignet (*Manuscrit 5*). Nous avons également comparé différentes approches qui ont été adoptées dans la

littérature pour évaluer la rigidité artérielle en utilisant la tonométrie d'aplanation, et avons révélé des différences cliniquement significatives dans la valeur de rigidité artérielle rapportée entre les méthodes (*Manuscrit 6*).

Ensemble, ces nouvelles contributions permettront a) d'orienter les recherches futures évaluant l'activité physique et la santé cardiovasculaire à l'aide de méthodes modernes, telles que l'accélérométrie et la tonométrie d'aplanation, et b) de faciliter l'élaboration de stratégies d'activité physique raffinées et durables pour lutter contre les niveaux élevés d'inactivité et les niveaux de risque cardiovasculaire élevé chez les personnes atteintes de maladies chroniques, c'est-à-dire l'hypertension, le DT2 et la maladie rénale chronique.

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LIST OF ABBREVIATIONS

AIx	Augmentation index
AIx75	Augmentation index corrected for a heart rate of 75 beats/minute
ACEi	Angiotensin converting enzyme inhibitor
ANCOVA	Analysis of covariance
AP	Augmentation pressure
ARB	Angiotensin receptor blocker
AS	Arterial stiffness
AUC	Area under the curve
baPWV	Brachial-ankle pulse wave velocity
BIC	Bayesian information criterion
BMI	Body mass index
BP	Blood pressure
BPM	Beats per minute
CAD	Canadian dollar
cfPWV	Carotid-radial pulse wave velocity
CI	Confidence interval
CKD	Chronic kidney disease
CO_2	Carbon dioxide
crPWV	Carotid-radial pulse wave velocity
CVD	Cardiovascular disease
ECG	Electrocardiogram
EE	Energy expenditure

ESRD	End-stage renal disease
eNOS	Endothelial nitric oxide synthase
GBTM	Group-based trajectory modeling
GFR	Glomerular filtration rate
HDL	High-density lipoprotein
HR	Heart rate
HOMA-IR	Homeostatic model assessment of insulin resistance
HTN	Hypertension
IPAQ	International physical activity questionnaire
IQR	Interquartile range
LDL	Low-density lipoprotein
LFE	Low frequency extension
MAP	Mean arterial pressure
MUHC	McGill University Health Centre
MVPA	Moderate-to-vigorous physical activity
NHANES	National Health and Nutrition Examination Survey
NO	Nitric oxide
O_2	Oxygen
OR	Odds ratio
PA	Physical activity
PPA	Pulse pressure amplification
PWA	Pulse wave analysis
PWV	Pulse wave velocity
RAAS	Renin angiotensin aldosterone system

RER	Respiratory exchange ratio
SD	Standard deviation
ST	Sub-theme
T2DM	Type 2 diabetes mellitus
VO_2 peak	Peak oxygen consumption
VSMC	Vascular smooth muscle cell

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First and foremost, I'd like to thank my principle supervisor, Dr. Stella Daskalopoulou, for her unwavering support and guidance throughout my time at the Vascular Health Unit. Her dedication to research and medicine is inspiring, and the generous time and energy she constantly provides to her students, while juggling many other commitments, never ceases to amaze me. I am enormously grateful for everything she has taught me, the challenges she has helped me to overcome, and the many opportunities she has provided that have enriched my training and ultimately, prepared me for the next steps. The Vascular Health Unit will always remain a very special place for me and I look forward to hearing about the many important accomplishments to come.

I also extend my sincere thanks to my co-supervisor, Dr. Kaberi Dasgupta, for her support, mentorship, and invaluable contributions towards my thesis. Her positivity and perseverance have motivated me greatly, and her insight and expertise has been appreciated at every turn.

I am grateful to my supervisory committee, Dr. Stephane Laporte, Dr. Ellen Rosenberg, Dr. Ross Andersen, Dr. Simon Bacon and Dr. Elham Rahme for their critical insight on my projects.

It was a great pleasure to work alongside Debbie Chan, Corinne Suppere, Marie-Eve Robillard, Sam Hajna, and Anne-Sophie Brazeau on the SMARTER trial. I thank them for their very hard work recruiting participants, running assessments, managing data, and making the SMARTER trial possible.

This experience would not have been the same without many friends and colleagues

at the Vascular Health Unit. They have been a vital support system over the years. I am grateful to my lab manager for many years, Yessica-Haydee Gomez, for her unconditional support, the countless hours spent patiently helping and teaching me, and her generous help with French translation. I also thank Alvin Kuate Defo, our research assistant, for his contribution to my projects and assistance at the lab, and Vincent Ta for his commitment to the PEDAL trial and his assistance recruiting patients, running assessments, coordinating volunteers and collecting data. I was fortunate to have worked with many bright and motivated volunteers at the lab who assisted with recruitment, assessment protocols, and data collection. A special thanks to Kim Phan and Jessica Gorgui for their friendship, endless support, and much needed culinary distractions.

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I am grateful to my thesis writing companion and dog, Millie. She has played a big role in helping me reach step count recommendations (rain/snow or shine) and the daily dose of love and silliness has provided more support than she knows.

Last, but not least, I thank my family, Chris, and close friends, for their continued love and encouragement throughout this degree and all my endeavors.

FORMAT OF THESIS

This thesis is organized as a manuscript-based thesis and follows guidelines outlined by the Faculty of Graduate and Post-Doctoral Studies of McGill University.

In **Chapter 1**, I introduce my thesis topic and state my thesis objectives. **Chapter 2** provides relevant background information for my thesis objectives. In **Chapter 3**, I present a summary of the methods used in my thesis. **Chapters 4-7** include individual publications of which I am the primary author:

Chapter 4 is based on two manuscripts that focused on the evaluation of a physician-delivered step-count prescription strategy among adults with hypertension and type 2 diabetes mellitus (*Manuscript 1 and 2*).

Chapter 5 presents the results of a pilot randomized controlled trial in a hemodialysis population evaluating the impact of intradialytic pedaling exercise on arterial stiffness (*Manuscript 3*).

Chapter 6 presents the findings from a study examining the impact of type 2 diabetes mellitus on the hemodynamic and vascular response to acute maximal exercise (*Manuscript 4*).

Chapter 7 is based on two manuscripts in which I evaluated methodological considerations for measurement of physical activity and arterial stiffness, the principal methods used in my thesis work (*Manuscript 5 and 6*).

In **Chapter 8**, I discuss the novel contributions of my thesis, as well as limitations and future directions.

ORIGINALITY OF WORK

This thesis is the result of my original work, carried out under the supervision of Dr. Stella Daskalopoulou (principal supervisor) and Dr. Kaberi Dasgupta (co-supervisor). The following are original contributions made by each manuscript:

Chapter 4

Manuscript 1: Cooke AB, Pace R, Chan D, Rosenberg E, Dasgupta K, Daskalopoulou SS. A Qualitative Evaluation of a Physician-Delivered Pedometer-Based Step Count Prescription Strategy with Insight from Participants and Treating Physicians. ***Diabetes Research and Clinical Practice*****. 2018 Mar 10; 139: 314-322**

This was the first study to explore barriers and facilitators influencing successful uptake and sustainability of a physician-delivered pedometer-based step count prescription strategy, from patient and physician perspectives. Our findings indicated that the framework for discussion, target setting, and accountability of the strategy could explain its ability to facilitate step count increases. The main barriers impeding improvements in step counts included health limitations, work constraints, and poor weather. The strategy was easily integrated into the patient-physician encounter but involvement of other members of the health care team is needed for maximal engagement and sustained use. This study will inform future studies in this area and the implementation of a step count prescription strategy into clinical practice.

Manuscript 2: Cooke AB, Rahme E, Kuate Defo, A, Chan D, Daskalopoulou SS, Dasgupta K. A Trajectory Analysis of Daily Step Counts During a Physician-delivered Intervention. Published in the ***Journal of Science and Medicine in Sport*****. 2020 Apr 18; electronic publication ahead of print.**

This study aimed to characterize the step count patterns over time in response to a physician-delivered step count prescription intervention. By using group-based trajectory modeling to identify distinct trajectories of step counts during the intervention, we were able to capture information about the variability of the response and established that a physician-delivered step count prescription and monitoring strategy appears useful across activity levels in adults with hypertension and/or type 2 diabetes mellitus (T2DM). Trajectory analysis is an under-utilized approach for examining the patterns of step count change that are otherwise lost when only the group mean is evaluated. Our findings highlight the value of using this approach in the context of a physical activity intervention.

Chapter 5

Manuscript 3: Cooke AB, Ta V, Iqbal S, Gomez YH, Mavrakanas T, Barre P, Vasilevsky M, Daskalopoulou SS. The Impact of Intradialytic Pedaling Exercise on Arterial Stiffness: A Pilot Randomized Controlled Trial in a Hemodialysis Population. ***American Journal of Hypertension*****. 2018 Mar 10; 31(4): 458-466.**

This study demonstrated that pedaling exercise during regular hemodialysis sessions is a safe and realistic means to help patients with chronic kidney disease achieve the arterial health benefits of increased physical activity. Through a 4-month randomized-controlled trial in patients on a stable in-center dialysis regimen, we demonstrated a clinically meaningful reduction in the "gold-standard" measure of arterial stiffness, as well as a reduction in heart rate. The decrease in arterial stiffness after pedaling exercise was partially reversed 4-months after exercise cessation, which reinforces the need for maintenance of regular physical activity in this population.

Chapter 6

Manuscript 4: Cooke AB, Dasgupta K, Spronck B, Sharman JE, Daskalopoulou SS. Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics. *Hypertension*. 2020 Apr 27; electronic publication ahead of print.

This was the first study to provide evidence of a greater increase in arterial stiffness in response to exercise among individuals with T2DM compared to those without T2DM, independently of the resting arterial stiffness. We also incorporated novel methods for evaluating a blood pressure-independent response of arterial stiffness. Our findings demonstrated that assessing the exercise-induced response of arterial stiffness provides additional information by capturing the effect of T2DM on the ability of the arteries to respond to increased demands during exercise. This is an important step in understanding the underlying hemodynamic mechanisms of the exaggerated blood pressure response in individuals with T2DM.

Chapter 7

Manuscript 5: Cooke AB, Daskalopoulou SS, Dasgupta K. The Impact of Accelerometer Wear Location on the Relationship between Step Counts and Arterial Stiffness in Adults Treated for Hypertension and Diabetes. J*ournal of Science and Medicine in Sport*. 2018 April 21; 21(4): 398-403

We were the first to evaluate the impact of wrist and waist accelerometer placement on the association between physical activity and a responsive arterial health indicator, carotid-femoral pulse wave velocity. We demonstrated differences in ActiGraph-derived physical activity measures between waist and wrist accelerometer locations, but also important differences in their relationship with carotid-femoral pulse wave velocity;

waist location accelerometer-derived physical activity signaled a relationship with the gold standard measure of arterial stiffness, but the wrist location did not. These findings add a new element to the evidence base supporting waist as the preferred accelerometer wear location in research and will hopefully inform the future design of studies involving physical activity measurement.

Manuscript 6: Cooke AB, Kuate Defo A, Lee J, Papaioannou T, Murphy J, Santosa S, Dasgupta K, Daskalopoulou SS. Methodological Considerations for the Measurement of Arterial Stiffness using Applanation Tonometry. Under revision at the *Journal of Hypertension.*

Different approaches have been adopted in the literature for collecting a reliable measure of arterial stiffness. I carried out the first study comparing different approaches currently used. We revealed clinically meaningful differences in the reported arterial stiffness value between methods. By disseminating these findings, we hope that researchers will consider methodological differences when comparing results across studies and be encouraged to follow a standardized protocol for their future studies.

All figures included this thesis are my original work, but it should be noted that I integrated some image vectors that were licensed from Adobe Stock. A standard license was obtained which permits their inclusion and modification in this thesis.

CONTRIBUTION OF AUTHORS

Manuscript 1

A Qualitative Evaluation of a Physician-Delivered Pedometer-Based Step Count Prescription Strategy with Insight from Participants and Treating Physicians.

Alexandra B. Cooke was directly involved in the qualitative study concept and method development, conducting the interviews, data acquisition, thematic analysis, interpretation and analysis of results, as well as the drafting of the manuscript. **Dr. Romina Pace** was responsible for conducting thematic analysis. **Deborah Chan** was involved in SMARTER trial execution and assisted with contacting participants for the interview. **Dr. Ellen Rosenberg** was involved in the SMARTER trial design and execution, as well as oversaw the qualitative analysis. **Drs. Kaberi Dasgupta** and **Stella Daskalopoulou** were responsible for the concept, design and execution of the SMARTER trial, and were involved in qualitative method development, and interpretation of results from thematic analysis. **All authors** participated in the critical revision and final approval of the manuscript.

Manuscript 2

A Trajectory Analysis of Daily Step Counts During a Physician-delivered Intervention.

Alexandra B. Cooke assisted with SMARTER trial execution and data acquisition and was responsible for developing the research question, conducting the study analysis/interpretation, as well as the drafting of the manuscript. **Dr. Elham Rahme** provided statistical input and assisted with the interpretation of results. **Alvin Kuate Defo** assisted with data collection and interpretation of results. **Deborah Chan** was involved in SMARTER trial execution, including collecting the log books that were used

for this analysis. **Drs. Kaberi Dasgupta** and **Stella Daskalopoulou** were responsible for the concept, design and execution of the SMARTER trial, provided valuable input during the analysis, and were involved in the interpretation of results. **All authors** participated in the critical revision and final approval of the manuscript.

Manuscript 3

The Impact of Intradialytic Pedaling Exercise on Arterial Stiffness: A Pilot Randomized Controlled Trial in a Hemodialysis Population.

Alexandra B. Cooke was responsible for study execution, data acquisition, interpretation and analysis of results, and drafting of the manuscript. **Vincent Ta** assisted with study execution, analysis of the results, and drafting of the manuscript. **Dr. Sameena Iqbal** was responsible for the concept, design, and oversight of the trial. **Dr. Iqbal** also facilitated communication with the dialysis team and collaborating physicians and was involved in the interpretation of results. **Yessica Haydee Gomez**, **Dr. Thomas Mavrakanas, Dr. Paul Barre**, and **Dr. Murray Vasilevsky** assisted with study execution and interpretation of results. **Dr. Stella Daskalopoulou** was involved in study concept and design, ethical approval, study execution, data acquisition, and interpretation and analysis of results. **All authors** participated in the critical revision and final approval of the manuscript.

Manuscript 4

Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics.

Alexandra B. Cooke assisted with SMARTER trial execution and data acquisition and was responsible for developing the research question, conducting study analysis/interpretation, as well as the drafting of the manuscript. **Dr. Kaberi Dasgupta**

was responsible for design and execution of the SMARTER trial and contributed to the interpretation of these results. **Dr. Bart Spronck** and **Dr. James E. Sharman** contributed to the interpretation of study results and proposed additional analytical approaches. **Dr. Stella Daskalopoulou** was responsible for study design, method development, and was involved in the interpretation of results, critical revision, and final approval of the manuscript. **All authors** participated in the critical revision and final approval of the manuscript.

Manuscript 5

The Impact of Accelerometer Wear Location on the Relationship between Step Counts and Arterial Stiffness in Adults Treated for Hypertension and Diabetes.

Alexandra B. Cooke assisted with SMARTER trial execution and data acquisition and was responsible for developing the research question, conducting the study analysis/interpretation, as well as the drafting of the manuscript. **Drs. Kaberi Dasgupta** and **Stella Daskalopoulou** were responsible for study design, method development, and were involved in the interpretation of results. **All authors** participated in the critical revision and final approval of the manuscript.

Manuscript 6

Methodological Considerations for the Measurement of Arterial Stiffness using Applanation Tonometry

Alexandra B. Cooke was responsible for the study concept and design, analysis, as well as the drafting of the manuscript. **Alvin Kuate Defo** and **Jeremy Lee** assisted with data collection. **Jessica Murphy, Dr. Sylvia Santosa, Dr. Kaberi Dasgupta**, and **Dr. Suzanne Morin** were responsible for the execution of studies from which the data was obtained. **Dr. Theodore Papaioannou** provided analytical suggestions and was involved

in the interpretation of results. All authors participated in the critical revision and final approval of the manuscript. **Dr. Stella Daskalopoulou** was responsible for study design, method development, was responsible for the execution of studies from which the data were obtained and was involved in the interpretation of results. **All authors** participated in the critical revision and final approval of the manuscript.

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CHAPTER 1: Introduction

1.1 Chronic Cardiometabolic Diseases and Cardiovascular Risk

The work included in this thesis focuses on the evaluation of physical activity promotion strategies aimed at improving cardiovascular health in adults with chronic disease, namely hypertension, type 2 diabetes mellitus (T2DM), and chronic kidney disease (CKD). These conditions share several risk factors, such as age, excess body weight, and physical inactivity[1], and their prevalence is increasing as a result of population aging, as well as shifts towards high energy diets and sedentary activities[2]. Hypertension, T2DM, and CKD are also interrelated in terms of their pathophysiology. T2DM and hypertension are both risk factors for CKD, and hypertension is twice as frequent in individuals with than those without T2DM[1]. Notably, all three conditions are linked to increased risk for cardiovascular disease (CVD), the leading cause of mortality worldwide, accounting for 40% of all deaths[3]. CVD encompasses a number of diseases affecting the heart and blood vessels, including coronary heart disease, cerebrovascular disease, peripheral artery disease, and atherosclerosis. Recent estimates from 2018 indicated that CVD is the 2nd leading cause of death in Canada, after cancer, and responsible for 23% of all deaths in Canada[4]. The economic burden of CVD on the Canadian health care system is upwards of 22 billion dollars annually, with additional costs for the individuals and their families[5].

Pharmacotherapies targeting cardiometabolic risk factors play a critical role in reducing CVD events and mortality in adults with hypertension, T2DM, and CKD. Lifestyle habits, such as healthy diet and physical activity are also important for optimal disease management, and when combined with pharmacotherapy, can lead to further improvements in CVD risk[6].

1.2 Physical Inactivity in Chronic Disease

Regular physical activity confers a wide range of cardiometabolic benefits, including higher insulin sensitivity, lower blood pressure, a more favourable lipid profile, and reduced arterial stiffening[7]. These benefits extend to populations with chronic diseases such as hypertension, T2DM and CKD, in whom regular exercise has been shown to reverse or slow disease progression and reduce the risk for CVD events and mortality[8]. Despite the many well-established benefits, engaging individuals with chronic disease to participate in regular physical activity can be challenging. Clinical guidelines recommend that adults undertake at least 150 minutes of moderate-to-vigorous physical activity (MVPA) each week[9-11]. However, accelerometer-based data from 2007 to 2017 indicate that less than 20% of Canadian adults achieve these recommendations[12]. Perceived lack of time, cost, health restraints, and lack of motivation and accountability are among the most commonly cited barriers to regular physical activity involvement[13]. Moreover, many individuals who begin an exercise program fail to maintain it in the long-term[14]. Thus, new strategies are needed to promote the incorporation of exercise into daily life, and that will encourage long-term adherence and engagement and translate to beneficial health outcomes. This thesis evaluates two different physical activity interventions integrated into clinical care: (1) a physician-delivered step count intervention in adults with T2DM and/or hypertension (SMARTER trial) and (2) an intradialytic pedaling intervention (PEDAL trial). My focus is on the assessment of arterial health impact and physical activity behavior.

1.3 Physical Activity Behavior

In the SMARTER randomized controlled trial, we evaluated the impact of physician-delivered step count prescriptions on arterial stiffness in adults with T2DM and/or

hypertension. Participants were provided with simple, low-cost pedometers to wear daily. Prescriptions with individualized daily step targets, gradually increasing over a 1-year period, were provided by the treating physician at each clinical visit. Compared to control arm participants, daily step counts increased by 1,200 steps in the active arm, and measurable improvements in glycemic control and insulin resistance were observed[15]. To date, the majority of prescription-based pedometer interventions, including the SMARTER trial, have quantitatively assessed the effectiveness of these interventions in terms of health outcomes and change in physical activity levels[15-18]. However, little is known about which aspects of a prescription-based pedometer strategy facilitate or hinder its successful application[19]. With the goal of widespread implementation of the strategy, this feedback is required to identify potential modifications to adapt the strategy to patients' needs and determine how it could be best implemented into clinical practice. This led us to conduct a qualitative study to explore participant and physician experiences during the trial, and perspectives on facilitators and barriers for uptake and implementation (*Manuscript 1*)[20].

Furthermore, the main results of the SMARTER trial focused on the mean change of steps over 1 year, a valuable metric for evaluating the effectiveness of the intervention on physical activity levels. Studying the patterns of step count change using step log data can offer additional information about the heterogeneity in the response of patients to this type of intervention. Therefore, we aimed to identify patterns of step count change in response to the SMARTER intervention and factors that influence the different responses (*Manuscript 2*).

1.4 Evaluating Impact on Vascular Health

Evaluating the cardiovascular benefits of physical activity using traditional metrics such as blood pressure can be challenging when blood pressure is well-controlled. For example, in patients adherent to antihypertensive treatments, blood pressure is often <130/90 mmHg and further possible reductions in blood pressure may not fully capture the vascular improvement attributed to physical activity. Arterial stiffening is an important risk factor for CVD, and the degree of stiffness has been shown to predict CVD events and mortality independently of traditional CVD risk factors, such as blood pressure[21-23]. Importantly, aerobic forms of exercise have been shown to lead to improvements in vascular function[24]. Therefore, the non-invasive measurement of arterial stiffness may provide us with a more responsive indicator of arterial health in a treated clinical population than traditional metrics. Arterial stiffness, assessed using applanation tonometry, served as the primary outcome in our pilot randomized controlled trial evaluating the cardiovascular health benefits of an intradialytic pedaling intervention in a population of adults with CKD on hemodialysis (*Manuscript 3*)[25].

Evaluating the exercise-induced response of arterial stiffness can also provide additional information about the ability of the arteries to respond to increased demands during exercise (referred to as the 'arterial stress test')[26]. The 'arterial stress test' served as a useful model in previous work involving young healthy smokers; we revealed an impaired ability of the arteries to respond to maximal exercise when compared to non-smokers[27]. During exercise stress testing, individuals with T2DM are more likely to experience an exaggerated blood pressure response[28], which is associated with higher CVD risk and mortality[29]. The mechanisms are not fully understood, but vascular abnormalities are thought to play an important role[30]. Therefore, we aimed to examine

the arterial stiffness and hemodynamic response to exercise in individuals with and without T2DM (*Manuscript 4*).

1.5 Methodological Considerations

Methods for the measurement of physical activity and arterial stiffness are evolving with technological advances and more widespread use in research and clinical settings. Pedometers and accelerometers are increasingly used to quantify physical activity levels in free-living settings and are superior to self report[31]. In the SMARTER trial, physical activity was assessed with waist-worn Yamax pedometers and GTX+ accelerometers. A subset of participants wore the accelerometer at the wrist, a placement location that is increasingly adopted for convenience purposes. However, studies comparing attachment sites have shown an overestimation of physical activity in both laboratory and free-living settings with wrist-worn devices[65], which may limit their utility for research and clinical purposes. To explore this issue further, we aimed to compare associations between physical activity measures derived from waist and wrist accelerometer locations with arterial stiffness, a variable previously shown to correlate with step counts in the SMARTER trial cohort (*Manuscript 5*)[32].

The evaluation of arterial stiffness has gained traction in various areas of research and is also being introduced into clinical settings to guide treatment decision-making[33]. Accurate comparisons of arterial stiffness within and across studies require standardized procedures. However, different approaches have been adopted in the literature for performing arterial stiffness measurements using applanation tonometry, the most widely used technique. This led us to compare the different approaches currently used and evaluate whether the choice of method can impact the arterial stiffness measure (*Manuscript 6*).

1.6 Thesis Objectives

The *overall aim* of this thesis is to evaluate the effectiveness of physical activity interventions integrated into clinical care in adults with chronic diseases, with a focus on the arterial health impact and physical activity behavior. Specifically, I aimed to:

(1) Contribute to our understanding of the effectiveness of a pedometer-based step count prescription strategy, and identify facilitators and barriers influencing uptake and implementation (*Manuscript 1 and 2*)

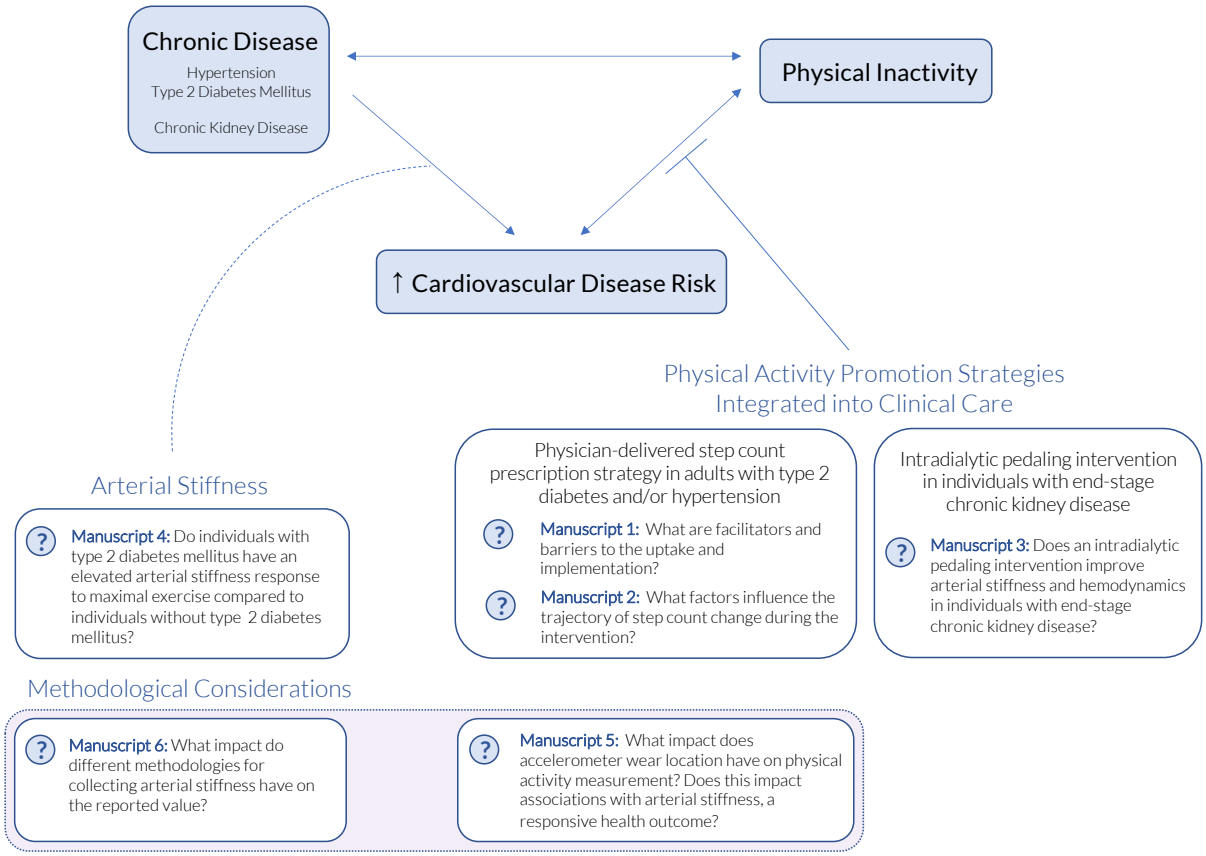
(2) Evaluate the arterial health impact of an intradialytic pedaling exercise intervention in adults with end-stage renal disease (*Manuscript 3*)

(3) Examine the impact of T2DM on the hemodynamic and vascular response to acute maximal exercise (*Manuscript 4*)

(4) Assess methodological considerations for the measurement of arterial stiffness and physical activity (*Manuscript 5 and 6*)

The following figure summarizes the central theme and objectives of this thesis.

Figure 1.1. Central Theme and Objectives of Thesis



CHAPTER 2: Thesis Background

2.1 Part 1: Physician-Delivered Step Count Intervention

The following section provides the relevant background information for the SMARTER trial, which evaluated the impact of step count prescriptions on physical activity levels and arterial health in overweight/obese sedentary adults with T2DM and/or hypertension.

2.1.1 Hypertension

Hypertension is a condition characterized by persistently elevated blood pressure [10]. According to Canadian blood pressure guidelines, thresholds for high blood pressure are systolic blood pressure (SBP) ≥ 140 mmHg or diastolic blood pressure (DBP) ≥ 90 mmHg when measured using a manual office blood pressure device and SBP ≥ 135 mmHg or DBP ≥ 85 mmHg when using an automated office blood pressure device[10]. Hypertension is the leading modifiable risk factor for CVD[34]. One in four Canadian adults aged 20-79 are reported to have hypertension[10,35], but the actual prevalence is likely higher as many individuals are asymptomatic and unaware that they have hypertension[36].

Elevated blood pressure increases the load on the heart, causing hypertrophy and dilation of the left ventricle, and eventually, a reduction in myocardial function[33]. Hypertension also triggers vascular injury, with detrimental effects on other end-organs, such as the kidney and brain[33]. Hypertension is a demonstrated risk factor for coronary heart disease, stroke, peripheral artery disease, and renal and heart failure[10].

Physical activity is important for the prevention and management of hypertension[10]. Regular participation in aerobic physical activity can elicit reductions in blood pressure[37]. Physical activity is inversely related to CVD mortality in the general population, but this also extends to individuals with hypertension; a systematic review of 6 studies including

96,073 individuals showed that compared to inactivity, any level of physical activity involvement was shown to decrease the risk of CVD mortality by 16-67%[38].

2.1.2 Type 2 Diabetes Mellitus

T2DM is a metabolic disorder characterized by chronic hyperglycemia resulting from insulin resistance and an insufficient insulin secretory response[39]. The diagnosis of T2DM is based on either: 1) a fasting plasma glucose ≥7.0 mmol/L, 2) a glycated hemoglobin A1c ≥ 6.5%, 3) a random plasma glucose level ≥ 11.1 mmol/L, and/or 4) a 2-hour plasma glucose value of ≥ 11.1 mmol/L in a 75g oral glucose tolerance test[40]. A confirmatory lab result is necessary unless the patient has symptomatic hyperglycemia. T2DM is largely preventable, as important risk factors are physical inactivity and excess weight, particularly in the abdominal region[40]. With rising obesity and sedentary behavior, the prevalence of T2DM has been increasing steadily[41]. In Canada, the age-standardized prevalence increased by 70% in one decade (1999-2009)[41]. According to the most recent estimates from 2013-2014, 3 million Canadian adults (8.1%) are currently living with diabetes, and 90% of these cases are T2DM[42].

T2DM is associated with a high prevalence of microvascular and macrovascular disease, involving small and large arteries, respectively[43]. Chronic hyperglycemia leads to the development of advanced glycation end products (AGEs), whereby glucose forms cross-links with amino acids on macromolecules[1]. Collagen, an important structural component of the arteries, is especially prone to these cross-links due to its long half-life, and the accumulation of AGEs within the vessels impacts the compliance of the arteries[44]. Hyperglycemia and insulin resistance also lead to increased levels of oxidative stress and inflammation, which both have detrimental effects on the arteries through increased endothelial and smooth muscle cell proliferation, hypertrophy, and remodeling[1]. As a

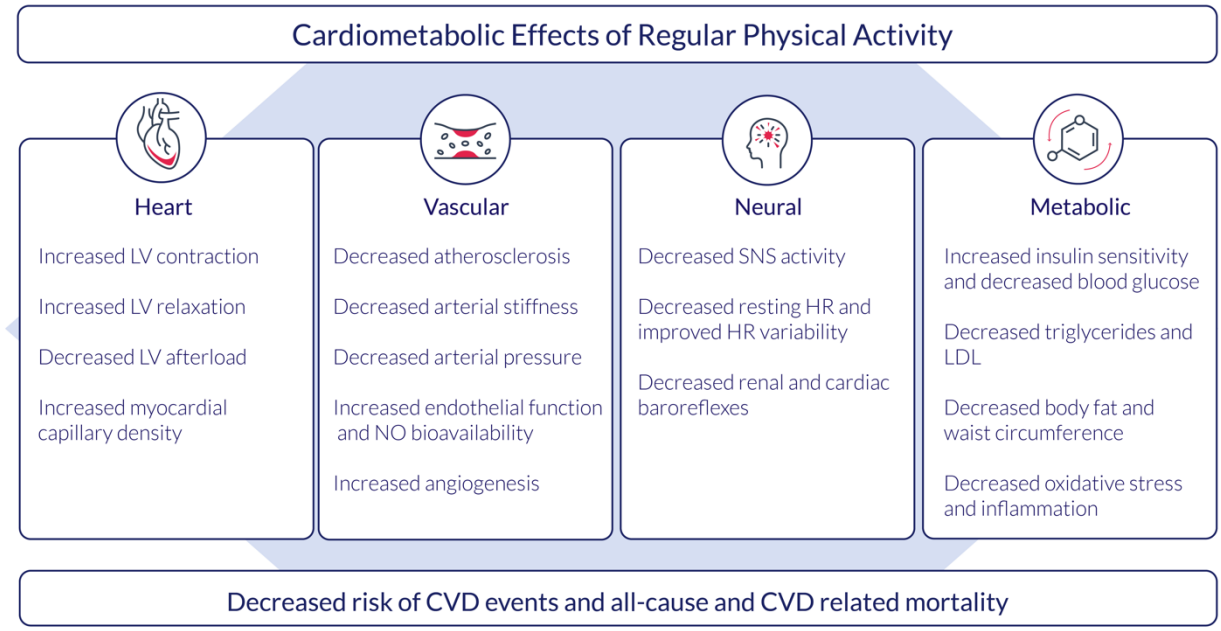
result, for many individuals with T2DM, their vascular age surpasses their chronological age[45], and they have a 2-4 fold greater risk of CVD than the general population, independent of other CVD risk factors[46-48]. There is also evidence to suggest that arterial stiffness is elevated before diabetes develops in individuals with high-normal fasting glucose levels when compared to individuals with low-normal glucose levels[49]. CVD accounts for the majority of morbidity and mortality in this population; individuals with hypertension at the time of T2DM diagnosis have a 57% and 72% increased risk of CVD events and all-cause mortality, respectively, when compared to normotensive subjects with T2DM[50]. Therefore, more intensive blood pressure treatment is advised in individuals with T2DM to reduce morbidity and mortality; Canadian guidelines suggest a target of <130/80 mmHg[10]. In addition to pharmacotherapy, regular participation in physical activity is recommended for blood glucose management in adults with T2DM[51,52]. Importantly, higher physical activity is associated with reduced CVD and all-cause mortality in individuals with T2DM[53,54]. These positive effects of physical activity have been shown to be independent of body mass index (BMI), cholesterol levels, blood pressure or smoking status[53].

2.1.3 Physical Activity and Cardiometabolic Health

Physical activity involves any type of bodily movement that increases energy expenditure and includes activities of daily living (e.g., climbing stairs, shoveling snow), while exercise is a planned, structured, and repetitive form of physical activity[55]. Both physical activity and exercise have been studied in relation to cardiometabolic health among individuals with hypertension and T2DM; however, the majority of studies have focused on improvements in response to exercise training interventions. While certain gaps in our understanding of the underlying mechanisms still exist, favourable cardiac

and vascular changes, as well as neural and metabolic adaptations have been well described[7]. From a vascular standpoint, regular physical activity leads to improvements in endothelial function, arterial stiffness, and blood pressure. The vascular changes that occur with physical activity, a central focus of this thesis, are discussed in greater depth in subsequent sections (2.3.5). The vascular improvements associated with regular exercise directly impact heart health through reductions in cardiac afterload, the pressure load the heart must overcome to eject blood[56]. Furthermore, repeated bouts of exercise can stimulate long-term improvements in cardiac structure and function, but this is more typically observed in response to higher intensity exercise[57]. Physical activity enhances glucose uptake by improving the responsiveness of the skeletal muscle to insulin through increased translocation of the glucose transporter protein, GLUT4[7]. Physical activity also promotes weight loss, thus counteracting the adverse effects of excess adipose tissue on insulin sensitivity. Reductions in sympathetic nerve activity and improvements in heart rate variability have also been documented[56]. Altogether, these improvements significantly lower the risk for CVD events and all-cause and CVD related mortality[56]. An overview of the main mechanisms by which physical activity improves cardiometabolic health are outlined in Figure 2.1.

Figure 2.1. Cardiometabolic Effects of Regular Physical Activity



HR, heart rate; LDL, low-density lipoprotein; LV, left ventricular; SNS, sympathetic nervous system
*The majority of the above-mentioned effects of regular physical activity have been observed in the context of exercise training interventions.

2.1.4 Health Benefits of Step Counts

Studies examining the impact of physical activity on cardiometabolic health and CVD risk have often examined more rigorous forms of leisure-time physical activity. However, it has been shown that even modest increases in walking, a convenient form of physical activity (defined as ambulatory physical activity), can lead to measurable benefits for individuals with hypertension and T2DM, including weight loss, improved fitness, lower blood pressure, and improved glucose control[58-60].

Step counts are a useful objective metric for quantifying the volume of ambulatory physical activity accumulated throughout the day. In a typical day, without deliberate

exercise, healthy adults achieve 6,000-7,000 step counts[61]. Moderate-vigorous physical activity for 30 minutes daily will add on average 3,000-4,000 steps/day, suggesting that individuals meeting physical activity recommendations would achieve ≥10,000 steps/day[61]. Individuals with step counts below 5,000 steps per day over a 21-day period are more likely to be classified as obese compared to those with step counts >9,000 steps/day[61]. Tudor-Locke and Bassett used this evidence to derive step count classifications, which have been widely applied to categorize physical activity levels using daily step counts[61]:

<5,000 steps/day	Sedentary
5,000-7,499 steps/day	Low active
7,500-9,999 steps/day	Somewhat active
10,000-12,499	Active
≥12,500 steps/day	Highly active

An extensive body of evidence, including large population studies such as the National Health and Examination Survey (NHANES), has demonstrated strong associations between daily step counts and cardiometabolic risk factors, including body composition (BMI and waist circumference), blood pressure, glucose control, insulin resistance, and cholesterol levels[62]. Specifically, in adults with impaired glucose tolerance, pedometer-assessed step counts showed an inverse association with the risk of CVD events over 6 years [hazard ratio (HR) 0.90, 95% CI 0.84-0.96, per 2,000 steps/day increment][63]. Importantly, a 2,000 steps/day increase over 1 year was associated with an additional 8% reduction in CVD events, adjusted for relevant confounders, including BMI change[63].

Small increments in step counts have also been associated with reduced mortality[64,65]. Among 16,741 older women who wore an accelerometer for 7 days as part of the Women's Health Study, walking as few as 4,400 steps/day was associated with a 41% reduction in all-cause mortality compared to women walking fewer than 1,700 steps/day (mean follow-up of 4.3 years)[65]. Importantly, increments as small as 1,000-steps/day were associated with a 15% reduction in mortality[65]. Furthermore, results from a large study in free-living middle-aged and older men and women demonstrated that any increase in steps over an average follow-up period of 3.7 years was associated with a 61% lower all-cause mortality compared to a decrease in steps, independently of age, sex, baseline step counts, and BMI change[64]. Several mechanisms are known to mediate the cardioprotective effects of ambulatory physical activity, including lower blood pressure and improvements in endothelial function and arterial stiffness[66].

2.1.5 Step Count Measurement

Well-known figures, including Leonardo da Vinci and Thomas Jefferson, have been credited with the invention of the pedometer. Leonardo da Vinci's version was designed for the Roman military in the 15th century to measure distance and improve the accuracy of their maps[67]. Thomas Jefferson introduced the pedometer to North America in the 18th century[68]. Known to enjoy walking, he sought to quantify the number of steps taken during his daily walks and commissioned a mechanical pedometer from a watch-maker in Paris[68]. Pedometers were first used to promote physical activity on a large-scale basis in the mid-1960s in Japan to combat rising obesity in the country[69]. The Japanese developed the first commercial waist-worn pedometer, which they called Manpo-kei, meaning "10,000 steps meter"[61]. The Japanese public was encouraged to walk 10,000 steps

per day which was believed to be the number of steps required to reduce the risk of CVD[69].

Physical activity monitoring devices have become increasingly more popular, user-friendly, and accessible in the 21st century. Pedometers continue to be used extensively as they provide an accountable and straightforward measure of step counts. A simple coiled spring-level mechanism responds to the up and down motion of each step and provides users with a count of steps taken on a digital screen[70]. Newer models have incorporated piezoelectric sensors to overcome the sensitivity of the pedometer to accurate positioning at the waist, as well as Bluetooth functionality to facilitate step count monitoring using a dedicated smartphone or online applications. Pedometers remain a very affordable ($20-25 CAD) means to measure daily step counts but they are limited in their ability to capture the intensity of movement.

Accelerometers provide another means for quantifying step counts. They utilize capacitance sensors to quantify acceleration along 3 reference axes (vertical, lateral, and longitudinal). A sinusoidal pattern of acceleration over time is observed during walking, and each peak in acceleration is reflective of a step[68]. In addition to step counts, they can be used to quantify physical activity volume and intensity, energy expenditure, as well as patterns of physical activity (ex. bouts) and periods of inactivity. The accuracy of these devices can vary between manufacturers as they all apply different proprietary algorithms to translate the acceleration into physical activity metrics. Research-grade devices, such as the ActiGraph GT3x, have been well-validated for use in many different patient populations. These devices are more costly (approximately $300 CAD), and not as practical for daily monitoring of step counts over an extended period of time.

Pedometers and accelerometers are typically worn at the level of the hip, closest to the body's center of gravity[31,71,72]. However, for convenience reasons, many accelerometers

are now being designed for the wrist, and many studies have switched to a wrist location to improve wear time compliance among participants[73]. For example, the wrist attachment site was used in the most recent cycle of the NHANES in the United States[73]. The wrist location has the advantage of allowing 24-hour monitoring and would prevent any misclassification of physical activity levels due to poor wear time[73]. Preliminary results (2011-2012) from the NHANES study indicated higher compliance rates of 70-80%, compared to 40-70% in previous cycles using waist-worn accelerometers[73,74]. However, studies comparing attachment sites have shown an overestimation of step counts in both laboratory and free-living settings[71], which questions the utility of wrist-worn devices for the accurate assessment of physical activity levels. We evaluated this further by assessing the impact of wear location on associations with a gold-standard vascular measure in *Manuscript 5*.

2.1.6 Pedometer- or Accelerometer-based Step Count Interventions

Step counting devices have enabled improvements in activity habits in the general population, as well as among individuals with chronic disease. A meta-analysis of eight clinical trials demonstrated that pedometer interventions were associated with a 2,491 daily step increase (95% CI 1098, 3885), a 3.8 mmHg (95% CI 1.7-5.9) decrease in SBP, and a 0.38 kg/m^2 (95% CI 0.05, 0.72) reduction in BMI[75]. It was also demonstrated that having a step count target was directly linked to increased physical activity levels[75]. Pedometer-based studies in T2DM have also shown improvements in physical activity levels[16,19,76-80], as well as hemoglobin A1c and fasting blood glucose[81].

Furthermore, step counters can facilitate greater incorporation of exercise into daily life and encourage the development of personalized strategies to increase walking that may be more sustainable in the long-term[14,70]. Interestingly, when compared to aerobic

fitness prescriptions, pedometer-based step count prescriptions (matched for total energy expenditure) were shown to lead to greater adherence over a 6-month period (92% vs. 77%)[14]. However, despite the convenience and improved adherence associated with walking, motivational support and accountability are still needed.

2.1.7 Step Count Prescriptions as a Physical Activity Promoting Strategy

In an effort to promote physical activity and behavioral changes in pedometer studies, various forms of physical activity counseling have been adopted. For the most part, studies have demonstrated greater improvements in step counts when counseling was provided, whether through group-based delivery, telephone or internet-based support, or individual consultations with behavioral experts[76-78,82,83]. However, these strategies can be cumbersome and difficult to sustain outside of a research setting.

In this context, physician-delivered step count prescriptions integrated into usual medical care visits would be less resource-intensive. Furthermore, this approach allows for greater continuity of physical activity monitoring, support, and accountability for patients, and has greater potential for widespread adoption[18,70]. The "Green Prescription" trial in New Zealand successfully increased walking time in sedentary older adults who were provided with an initial prescription from their primary care physician and follow-up by a physical activity counselor over 1 year[18]. Interestingly, they showed that step-based prescription led to a greater increase in walking time than a time-based prescription (50 minutes/week vs. 28 mins/week). Other pedometer intervention studies integrated into primary care have demonstrated improvements in physical activity levels among older sedentary adults when nurses were responsible for delivering the physical activity consultations[83].

2.1.8 Prescribing Exercise from the Physicians' Perspective

Physicians understand and value their role as advocates for physical activity promotion[84-86], but they have emphasized challenges in achieving sustainable behavioral change[84]. In fact, one survey-based study showed that only 5.3% of physicians felt they could successfully change patients' physical activity behaviors[87]. Clinical guidelines provide physicians with clear recommendations for their patients regarding the amount they should be exercising (time-based goals) and more recently, have encouraged a prescription approach[9-11]. A number of qualitative studies have explored the attitudes and experiences of physicians associated with advising patients about physical activity during routine consultations[84]. While the majority of physicians expressed positive views about health promotion, commonly cited barriers included a lack of knowledge about approaches to elicit behavioural change, as well as lack of resources, effective tools, time, and training[84,88]. Most importantly, they have expressed that general advice about current exercise recommendations or even time-based exercise prescriptions does not support the individual needs of chronically ill patients. As a result, they have emphasized the need for more realistic and individualized strategies[84,86,88].

2.1.9 The SMARTER Trial

SMARTER, a CIHR-funded randomized controlled trial, aimed to address this need by examining the arterial health and physical activity behavior impact of a pedometer-based step count prescription strategy delivered by the treating physician and incorporated into routine care in patients with T2DM and/or hypertension[89]. Active arm participants were provided with simple, low-cost pedometers to wear daily. Written prescriptions with individualized daily step targets, gradually increasing over a 1-year period, were provided by the treating physician at each clinical visit, every 3-4 months.

The overall goal was a net increase of 3,000 steps/day above baseline over 1 year, and the rate of increase was tailored to each participant's baseline activity level. Control arm participants received their usual care advice. Compared to control arm participants, daily step counts increased by 1,200 steps in the active arm. Arterial stiffness was reduced in the active arm by 0.3 m/s when compared to the control arm, but was not conclusive (95% CI -0.74, 0.14). Power calculations were based on changes in arterial stiffness in response to an aerobic exercise intervention (only available study in adults with T2DM and hypertension). More recent data from a meta-analysis of supervised exercise interventions reported a much smaller change in arterial stiffness suggesting that the estimates used in power calculations were an overestimation of the change one would observe in response to a modest increase in steps[24]. Interestingly, conclusive improvements in glycemic control and insulin resistance were observed. Participants who received the step count prescriptions had a greater reduction in hemoglobin A1c [0.38% (95% CI -0.69, -0.06), assessed only in T2DM] and homeostatic model assessment of insulin resistance (HOMA-IR) [0.96 (95% CI -1.72, -0.21), assessed in participants not treated with insulin] when compared to control arm participants[15]. I participated in the arterial stiffness and stress test evaluations for SMARTER and co-authored this publication[15]. My involvement and interest in the SMARTER trial led me to conduct the secondary analyses in *Manuscripts 1, 2, 3 and 5.*

Objective measurements of daily steps/day over a 1-week period were obtained at baseline and at 1-year in both active and control arm participants. Active arm participants further logged their daily step counts in a step count log. The main results of the SMARTER trial focused on the mean change of steps over 1 year, a valuable metric for evaluating the effectiveness of the intervention on physical activity levels. However, evaluating the patterns of step count change using step log data can offer additional

information about the heterogeneity in the response of patients to this type of intervention, and the factors that influence this response. Group-based trajectory modeling (GBTM) is a useful longitudinal statistical modeling approach that identifies groups that follow statistically similar trajectories over time[90]. Rather than assuming a "fit all" trajectory shape, any variability in the response over time can be captured by identifying trajectories that differ in terms of their shape or level. Identifying different trajectories will allow us to evaluate predictors of the step count response to the intervention to understand which subgroups were most responsive. This will enable us to improve the intervention. Therefore, we explored trajectories of step counts in response to the SMARTER intervention in *Manuscript 2*.

To date, the majority of prescription-based pedometer interventions, including the SMARTER trial, have quantitatively assessed the effectiveness of these interventions in terms of health outcomes and change in physical activity levels. A limited number of studies have explored the experiences of end-users involved in a pedometer-based intervention delivered in a primary care setting[13,83,91]. Harris and colleagues interviewed 30 older adults after a 12 week intervention consisting of four tailored physical activity consultations with a practice nurse, with monitoring of step counts during the PACE-lift trial[83]. Participants and trial nurses were enthusiastic about the intervention components (pedometer, nurse consultations, a handbook for graphing step progression). Barriers included weather and existing health conditions. While SMARTER benefits were observed at 1-year after a 12-month intervention, the PACE-lift trial benefits were observed at 12 weeks, but the intervention was not sustained, and no differences were observed at 1-year. This may be explained by the fact that in the PACE-list trial the four nurse consultations took place in the first 10 weeks, and participants had no source of follow-up for the remainder of the trial. Feedback from physicians and patients regarding

the incorporation of a physical activity promotion strategy into regular clinic visits is required to determine whether this may be a more sustainable approach. This would also allow for the identification of potential modifications to adapt the strategy to patients' needs and determine how it could be best implemented into clinical practice. Therefore, we carried out a qualitative evaluation of the SMARTER trial in *Manuscript 1*.

2.2 Part 2: Intradialytic Pedaling Intervention

The following section provides the relevant background information for the PEDAL trial, which evaluated the impact of intradialytic pedaling exercise on arterial health in individuals with CKD receiving in-center hemodialysis treatment.

2.2.1 Chronic Kidney Disease

CKD is a chronic condition characterized by the presence of kidney damage or reduced kidney function, preventing adequate elimination of excess fluid and metabolic waste products[92]. The severity of CKD is classified based on the glomerular filtration rate (GFR), and the level of albuminuria. GFR is estimated from an individual's creatinine clearance adjusted for age, sex, and body weight (termed eGFR), and is considered an accurate indicator of overall kidney function[92]. Albuminuria reflects increased glomerular permeability and is assessed by calculating the albumin-to-creatine ratio in the urine. Higher levels of albuminuria have been associated with increased mortality risk and progression of CKD, independently of eGFR[93]. Specifically, in earlier stages of the disease, albuminuria was shown to be more predictive of renal and CVD events than eGFR. Therefore, both factors are considered when establishing the level of risk for CKD progression and complications[92].

End-stage renal disease (ESRD) occurs when renal function deteriorates to the extent that renal replacement therapy (i.e., hemodialysis, peritoneal dialysis, or a kidney transplant) is required[92]. Routine hemodialysis allows for excess fluid and metabolic waste products to be cleared from the blood[94]. The frequency of hemodialysis depends on a number of factors, including the severity of the disease and body size, but most often, patients will undergo hemodialysis treatments 3 times a week for 3-4 hours[94]. Due to the shortage of available kidney transplants, limited graft survival, and ineligibility of some

patients e.g., in the presence of comorbidities, ESRD patients often require dialysis, and the majority will be placed on hemodialysis[95]. The prevalence of ESRD is rising rapidly in response to the ageing population and increasing rates of diabetes and hypertension[96]; in Canada, the number of individuals with ESRD on dialysis number rose by 31% over a 10-year period[97]. Despite advances in treatment and renal replacement therapies, individuals with ESRD have a greatly reduced lifespan, largely due to CVD, the leading cause of morbidity and mortality in this population[98].

2.2.2 Cardiovascular Risk in Chronic Kidney Disease

CVD mortality risk increases in a linear fashion with decreasing GFR[98]. Among individuals with ESRD receiving dialysis, over 50% have CVD, and their level of CVD-mortality risk is 10-20 times greater than the general population[98]. While traditional CVD risk factors such as obesity, hypertension, diabetes, and dyslipidemia are more prevalent in patients with CKD, not all of the CVD risk can be attributed to these traditional risk factors[98]. A portion of the CVD risk is associated with damage caused by factors associated with renal insufficiency, such as uremic toxins and volume expansion, as well as abnormalities related to bone and mineral metabolism[98].

Elevated arterial stiffness is thought to contribute to the elevated CVD risk in this population[99]. Patients with CKD are known to have an accelerated stiffening of the arteries, which in part is driven by the high prevalence of hypertension[99]. However, altered bone and mineral metabolism and greater retention of calcium lead to greater calcification of the arteries[99]. Elevated serum phosphate levels trigger vascular smooth muscle cells (VSCMs) to take on osteoblast-like phenotype which produces fibrotic extracellular matrix leading to arterial thickening and stiffness[98]. Furthermore, the healthy kidney is an important source of antioxidant enzymes, and thus the progression

of kidney failure has been shown to lead to an accumulation of reactive oxygen species and thus, oxidative stress[98]. Oxidative stress is particularly harmful to the vascular endothelium, as it reduces the overall synthesis and bioavailability of nitric oxide (NO), an important modulator of vascular tone[100]. Higher levels of asymmetric dimethylarginine, an endogenous inhibitor of endothelial NO synthase (eNOS), have been reported in ESRD and is implicated in the progression of endothelial dysfunction through its impact on NO synthesis[98]. The process of hemodialysis in itself promotes the accumulation of oxidative products, as well as the loss of anti-oxidants as the blood is filtered[98]. Overall, the presence of oxidative stress, and reduced NO synthesis and bioavailability directly contributes to endothelial dysfunction and increased vasoconstriction of the arteries[101]. Levels of inflammatory molecules such as transforming growth factor β, C-reactive protein, tumor necrosis factor-α and interleukin-6 are known to be elevated in ESRD patients and correlated with central arterial stiffness[102]. The degree of arterial stiffness has been shown to have predictive value for CVD events and mortality in ESRD patients, independently of traditional cardiovascular risk factors[103,104].

2.2.3 Physical Inactivity in Chronic Kidney Disease

As previously discussed (section 2.1.3), regular physical activity plays an important role in reducing CVD risk. However, individuals with CKD receiving hemodialysis are generally less physically active and have lower physical functioning compared to age-matched healthy individuals[105]. Physical limitations, such as reduced muscle mass, neuropathy, and cardiovascular limitations, combined with depression and lower quality of life, negatively affect physical activity levels[106]. Additionally, the initiation of dialysis has been shown to lead to a significant reduction in physical function, independently of age, sex, ethnicity and baseline functional status[107]. Among individuals with CKD,

physical function, aerobic capacity, and overall physical activity levels are strong predictors of survival and associated with risk for CVD events[108,109]. Among 2,507 hemodialysis patients, Stack and colleagues demonstrated that regular aerobic exercise involvement 2-3 times per week was associated with a 26% lower risk of mortality[110]. However, adherence to regular exercise is especially poor in this population[111,112]. According to this same study, only 20% of participants exercised daily, and 56% of participants reported exercising less than once a week[110]. For many patients, a large portion of their week is spent attending dialysis treatment thus reducing time for physical activity involvement.

2.2.4 Physical Activity Interventions in CKD Populations

Different physical activity promotion strategies have been tested, which have involved group training programs or walking interventions at home, as well as physical activity programs incorporated into the dialysis visit. Systematic reviews of aerobic exercise interventions in a hemodialysis population have shown benefits with regards to improving aerobic fitness, physical function, and quality of life[112,113]. Few studies have examined the cardiovascular health impact of aerobic exercise[114-117]. A randomized controlled trial evaluating a 1-year lifestyle program involving aerobic and resistance training versus usual care did not observe any conclusive changes in blood pressure, but showed attenuation of the change of arterial elastance, a measure of the arterial load[117]. Interestingly, Mustafa and colleagues observed an improvement in the augmentation index (AIx), a measure of arterial pressure wave reflection, after 3 months of supervised aerobic exercise using a treadmill or recumbent bike (two sessions of 60 minutes/week) in 11 hemodialysis patients at a cardiac rehabilitation centre[115]. In a separate investigation, they found similar reductions in AIx in response to supervised and home exercise (3

sessions of 60 minutes/week) in 20 pre-dialysis patients[116]. While these interventions have shown promise for arterial health improvements with exercise, supervised aerobic exercise programs requiring specialized equipment are resource-intensive and challenging to maintain in the longer-term.

Intradialytic pedaling exercise is gaining support as a more realistic exercise intervention for hemodialysis patients. Simple ergometers are placed in front of or attached to the dialysis chair, allowing participants to pedal during their dialysis sessions while seated or lying down. It has the advantage of being performed in a supervised setting, requires no additional time commitment outside of dialysis, and is considered feasible for the many hemodialysis patients with functional limitations that would prevent more rigorous forms of aerobic exercise[118]. Intradialytic pedaling exercise is also considered to be safe for hemodialysis patients. A negligible number of adverse events have been reported in studies; a systematic review of 27 trials and 1215 participants reported only 4 events, which included hypoglycemia, limb pain, or minor injury[119]. Patients will typically spend 3-6 hours on three days a week in the dialysis unit, which provides an ideal time to engage patients and help them achieve physical activity recommendations.

A systematic review and meta-analysis of 17 intradialytic pedaling exercise interventions in hemodialysis patients (n=651) demonstrated improvements in Kt/V (clearance of urea over dialysis time, provides a measure of dialysis adequacy), VO_2 peak, quality of life (physical component), and depression[120]. While changes in blood pressure have not been reported[121], there is evidence from one study suggested that a 3-month intradialytic pedaling exercise may impact carotid-femoral pulse wave velocity (cfPWV), the 'gold-standard' measure of central arterial stiffness. They reported a 1.7 m/s decrease in in the exercise group (n=9) and a 1.7 m/s increase in the control group (n=10) during

the first 3-month intervention period; however, the results in both groups were not conclusive[122]. A substantial limitation of this study was the fact that the study only presented within-group changes in the control group and exercise group but did not consider between-group changes (exercise group vs. controls). Although limited, these preliminary findings suggesting possible arterial health benefits motivated our group to explore this further in our PEDAL randomized controlled trial. We examined the impact of a 4-month intradialytic pedaling intervention on arterial stiffness and hemodynamics in *Manuscript 3.*

2.3 Part 3: Evaluation of Cardiovascular Health with Arterial Stiffness

The investigation of arterial stiffness has gained momentum in the last 30 years with the development of relatively simple non-invasive techniques and mounting evidence regarding its predictive value for CVD and mortality[21-23]. It is generally accepted that traditional risk factors (e.g., blood pressure, cholesterol, glucose, BMI) do not fully explain CVD risk; a number of other non-traditional factors are at play, including inflammation, oxidative stress, endothelial dysfunction, vascular wall abnormalities, insulin resistance. The degree of stiffness of the arteries is thought to reflect the cumulative impact of these cardiovascular risk factors and their interactions on the arteries over time, and thus, provides a summative measure of arterial health. This not only adds value to the assessment of cardiovascular risk, but also, may provide a more responsive measure than traditional methods when evaluating cardiovascular health improvements in response to exercise[22]. Moreover, the majority of existing pharmacological approaches for treating hypertension do not directly target arterial stiffness[33]. Therefore, the non-invasive measurement of arterial stiffness also provides a responsive indicator of arterial health in a treated clinical population.

2.3.1 Arterial Stiffness

The arterial pulse has been studied for centuries. As early as the Middle Ages, physicians established the connection between the arterial pulse and the elasticity and resistance of the arteries and began to examine the pulse for both diagnosis and prognosis[123]. The modern era of medicine saw the development of measurement devices, such as the sphygmometer, that could quantify characteristics of the pulse, including its force, rhythm and regularity[123]. Important contributions towards the analysis of the

arterial pressure wave were made in the 19th century, including the development of the sphygmograph by Marey in 1860, which enabled non-invasive graphical recordings of the pressure wave[124]. However, when Riva-Rocci developed the modern mercury sphygmomanometer in the early 20th century, a simpler and more comfortable device for patients, the focus shifted towards the two blood pressure extremes, SBP and DBP[124]. Blood pressure was established as an important risk factor for CVD, and blood pressure measurement was widely adopted in clinical practice. It is only in the last 30 years that researchers have rediscovered the wealth of information that can be obtained by studying the propagation and shape of the arterial pressure waveform as it travels through the arterial tree. The development of non-invasive methods for the measurement of arterial stiffness and central hemodynamics has enabled important advances in our understanding of arterial physiology and the pathophysiological mechanisms of a number of diseases involving the arteries, including hypertension, T2DM, and CKD. Arterial stiffening is now widely acknowledged as an important mediator and risk factor for CVD and the degree of central arterial stiffness has been shown to have independent predictive value for CVD events and mortality in a wide range of patient populations[21-23].

2.3.2 Determinants of Arterial Stiffness

Arterial stiffness reflects the rigidity of the artery wall. The rigidity at any given point is influenced by the interaction between the structural composition of the artery wall and transient functional elements[33]. This interaction between structural and functional components is also influenced by various extrinsic factors, as well as the distending pressure[125].

2.3.2.1 Structural Component

The structural integrity of the arteries largely depends on the interplay between elastin, collagen and VSMCs within the artery wall[125]. Elastin is much more extensible than collagen. Elastin enables the arteries to stretch and recoil with cyclic changes in pressure, and collagen provides structural support and protects the artery against excessive stretch at high pressures. The composition of the arterial segments changes to accommodate their different functions. For example, the elasticity of the central arteries (e.g., aorta) is the result of a high elastin:collagen ratio; however, this ratio diminishes gradually towards the periphery as the arteries become more muscular (e.g., radial artery)[125]. VSCMs are the predominant cell type in the arteries and play an important role in controlling vessel diameter and tone[125].

With healthy aging, the elastin:collagen ratio becomes disrupted due to the gradual fragmentation and degradation of elastin fibers, as well as an abnormal accumulation of collagen[125]. Elastin synthesis occurs only during development, and therefore any degradation cannot be restored. Conversely, collagen content in the arteries has been shown to double between 20 and 70 years[126]. Collagen is susceptible to non-enzymatic glycation cross-linking, which leads to a stiffer collagen fiber, slower turn over, as well as a more disorganized fiber distribution[125]. A stiffened vessel typically also exhibits VSMC hypertrophy and proliferation, as well as a greater number of cell adhesion molecules, macrophages, and other inflammatory cells[125].

The proximal aorta is most susceptible to stiffening with age[127]. As a result, cfPWV, a measure of central arterial stiffness, has been shown to increase by 0.2-0.7 m/s every 5 years in healthy individuals, and at an even faster rate after the age of 60 years[128]. As previously mentioned, hypertension and diabetes (T2DM, as well as type 1 diabetes

mellitus) significantly accelerate age-related stiffness; however, other risk factors including smoking, dyslipidemia, sedentary lifestyle, high salt intake are also implicated[21].

2.3.2.2 Functional Component

In addition to structural changes, arterial stiffness is also influenced by functional changes within the artery[129]. For example, smooth muscle tone is regulated extrinsically by the sympathetic nervous system and locally through various vasoactive mediators such as NO, endothelin-1, and prostanoids[129].

NO is especially critical for regulating vascular tone, acting as the most potent vasodilator. NO is formed in endothelial cells from its precursor L-arginine via the enzymatic action of eNOS. Shear stress, the frictional force of blood against the endothelium, is a key stimulator of eNOS, leading to higher levels of NO during and after exercise[130]. NO stimulates the relaxation of VSCMs but also exhibits a number of anti-atherogenic properties, including the prevention of platelet activation, the inhibition of VSMC proliferation and migration, leukocyte activation/adhesion, and oxidation of low-density lipoprotein[131]. Furthermore, NO plays an essential role in counterbalancing endothelin-1 levels, a potent vasoconstricting peptide, by inhibiting its synthesis in endothelial cells[132]. Prostanoids such as prostacyclin and thromboxane A_2 are also involved in regulating vasodilation and vasoconstriction, respectively, and have opposing effects on platelet aggregation[133].

A tightly controlled balance between opposing vasodilating and vasoconstricting factors is essential to maintaining endothelial integrity and vascular function[129]. When this balance is disrupted, the arteries lose their ability to vasodilate in response to vasodilatory stimuli or shear stress. The vasculature also becomes more susceptible to

platelet activation, leukocyte adherence, impaired coagulation, thrombosis, and vascular inflammation[134]. This impaired state is known as endothelial dysfunction and recognized as an important determinant of arterial stiffness. Conversely, it has also been shown that arterial stiffness can alter endothelial function, which in turn accelerates the stiffening process, creating a vicious cycle of arterial dysfunction[135].

2.3.2.3 Extrinsic Factors

Several hormones can modulate the structure and function of the arteries. Angiotensin II, a potent vasoconstrictor, and the primary effector of the renin-angiotensin-aldosterone system (RAAS) has been shown to increase oxidative stress, and impair NO synthesis[125]. Structurally, angiotensin II stimulates collagen formation, VSMC proliferation and hypertrophy, and matrix remodeling[125]. High insulin levels lead to alterations in RAAS activity, and increased angiotensin II levels, as well as vascular wall hypertrophy and fibrosis[136]. Other hormones shown to influence arterial stiffness include thyroid hormones, sex hormones, and prolactin[136]. Dietary sodium has also been shown to impact arterial stiffness, independently of blood pressure change, by triggering oxidative stress within the vascular wall and reducing NO bioavailability[137].

2.3.2.4 Blood Pressure

The elasticity of the arteries is also dependent on the pressure within the artery[129]. Arterial stiffness is represented by the slope of the exponential relationship between stress (change in pressure) and strain (change in arterial diameter) at any given point. The relationship between stress and strain in the artery wall is never constant, as the material properties of the wall change with distending pressure. At low distending pressures, elastin fibers stretch to absorb the pressure; but at higher distending pressures, the inelastic collagen fibers are engaged, which increases the arterial stiffness[125]. This shift

occurs to control the amount of strain for a given stress, which can occur temporarily in response to acute increases in blood pressure, such as with exercise. However, chronic elevations in blood pressure lead to a more permanent stiffening of the arteries. While stiffness can be restored to some extent with blood pressure lowering, increases in stress over time stimulate the production of collagen and fragmentation of elastin fibers leading to irreversible reductions in the elastin:collagen ratio[33].

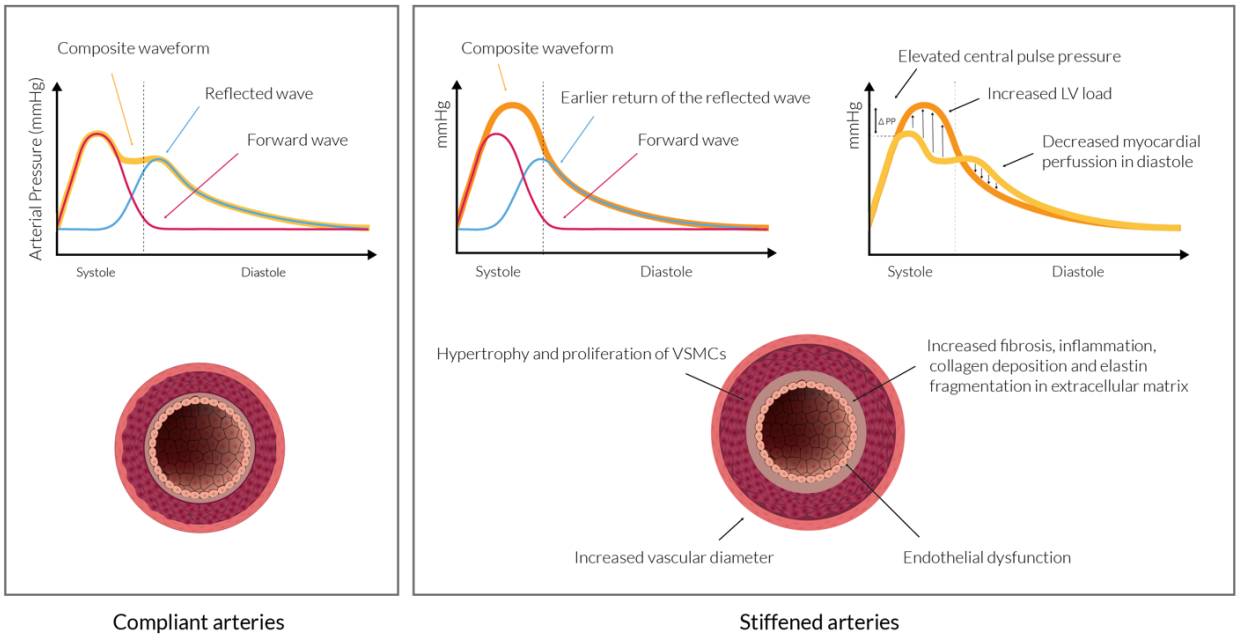
2.3.3 Consequences of Arterial Stiffening

Changes to structural and functional components of the arteries impact two critical functions. Through their vast network in the body, arteries distribute oxygenated blood to peripheral tissues. They are highly adaptable to changes in blood flow and involved in the redistribution of blood to different parts of the body as needed. The arteries also play an important role in buffering the cyclical changes in blood pressure caused by the intermittent ejection of blood from the heart. The elasticity of the proximal aorta enables it to act as a second pump by momentarily storing about 50% of the stroke volume during systole, and then releasing the blood upon recoil during diastole[138]. Through distension, the artery is effectively storing kinetic energy produced by the heart as potential energy, which is subsequently released during diastole, propelling the accumulated blood forward[138]. This phenomenon, known as the Windkessel effect, ensures a steady flow of blood and pressure towards the periphery[138]. This term is derived from the Windkessel system in old fire engines, where a secondary chamber with compressed air was used to convert the intermittent flow of water to a more continuous steady flow[139]. The efficiency of this function is compromised by the stiffening of the arteries. When the artery loses its ability to expand during systole, a greater proportion of the stroke volume is released to the periphery, and it cannot dampen the fluctuation in pressure, leading to a widened

pulse pressure[138]. This has detrimental consequences on the heart, as well as the microcirculation and end-organs.

The stiffness of the arteries also determines the morphology of the arterial pressure wave, as depicted in Figure 2.2.

Figure 2.2. Morphology of the Arterial Pressure Wave in Compliant and Stiffened Arteries

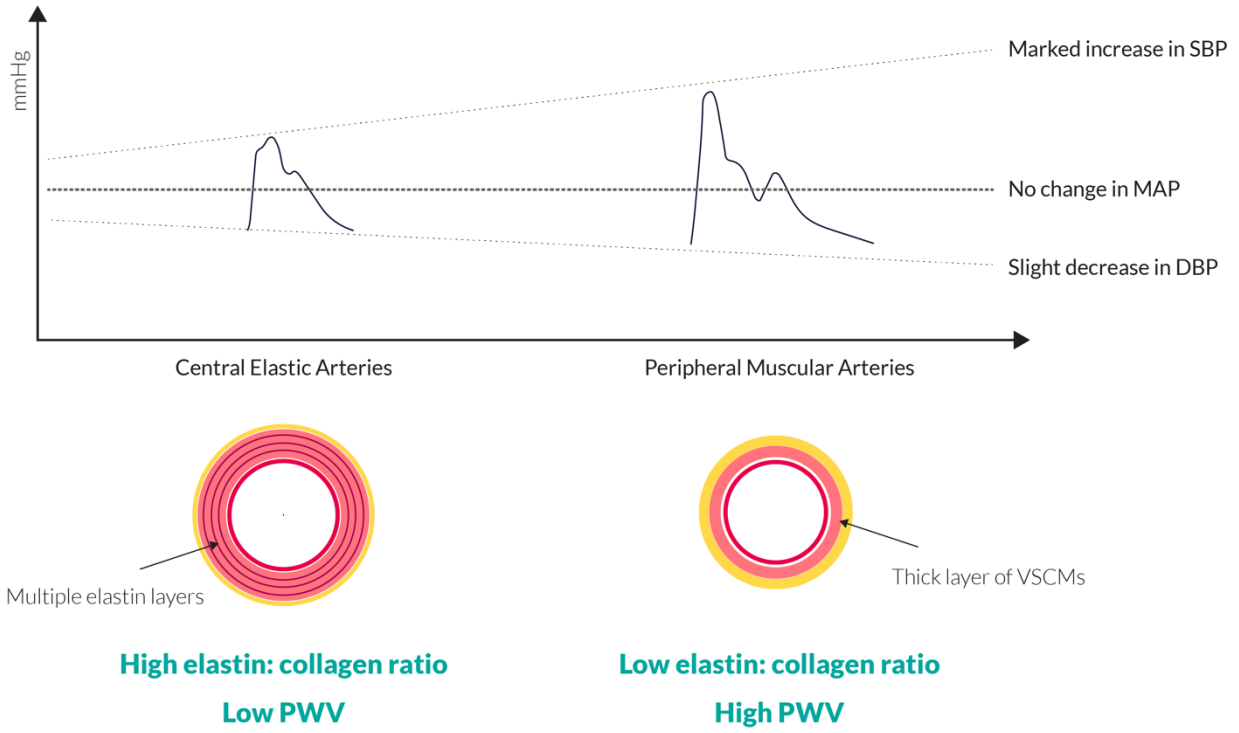


With each ventricular contraction, a pressure wave is generated within the aorta and travels down the arterial tree. When the forward traveling waves encounter sites of impedance mismatch such as bifurcations, narrowing of the artery, and changes in arterial composition and stiffness, a series of reflected waves are formed, traveling back towards the heart. The interaction between the forward and reflected waves creates a composite arterial pressure waveform, and its shape depends on the timing of this interaction. The viscoelastic properties of the aorta determine the speed at which the pressure waves travel, or pulse wave velocity (PWV). In elastic arteries, the pressure

wave will travel more slowly, and the reflected waves interact with the forward wave mainly during diastole. This leads to a slight increase in central DBP and supports the healthy perfusion of the myocardium. However, loss of elasticity within the artery increases the speed at which the pressure wave travels, causing the reflected wave to arrive earlier during the cardiac cycle. Consequently, the reflected wave becomes superimposed mainly on the systolic part of the forward wave, leading to elevated central SBP, and a widened pulse pressure. This increases the ventricular load and reduces the favourable coronary artery perfusion during diastole, predisposing the heart to left ventricular hypertrophy, ischemia, and ultimately, failure[33].

The morphology of the waveform changes as it reaches the peripheral arteries due to the gradual stiffening of the vessels as they extend from the heart. As previously mentioned, this is due to the greater presence of VSMCs in the peripheral arteries[138]. Therefore, the higher PWV in these segments, combined with the closer proximity of the reflected sites (branching of many small arteries), causes the reflected wave to arrive earlier during systole[138]. This phenomenon, depicted in Figure 2.3, is known as pulse pressure amplification and leads to higher SBP and pulse pressure in the arm compared to centrally[138].

Figure 2.3. Pulse Pressure Amplification Phenomenon



With aging and increases in central arterial stiffness, the central SBP increases, and the healthy gradient between central and peripheral pressures is lost (i.e., a reduction in pulse pressure amplification is observed). This diminishes distal wave reflection and leads to the greater transmission of the forward wave and associated pulsatile energy to the microvasculature. The low resistance vessels of the kidney and brain are particularly vulnerable to this pulsatility, which results in structural damage and diminished functional capacity of these organs.

Due to this amplification phenomenon, it is now recognized that conventional peripheral (brachial) blood pressure is not always a reliable measure of blood pressure load at the level of the heart[129]. Hypertension medications can have differential effects on central and peripheral blood pressure, and therefore, important information may be overlooked when only measuring peripheral blood pressure. This first came to light in

the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), which demonstrated a greater reduction in CVD events in patients with hypertension receiving vasodilator drugs (calcium channel blockers with or without angiotensin-converting enzyme (ACE) inhibitors) compared with patients treated with non-vasodilators (β-blocker with or without a diuretic), but no group differences in the reduction of peripheral blood pressure were noted[140]. Further analysis in a subgroup of participants with central BP measures (CAFE arm of ASCOT trial) showed that the decrease in central SBP and pulse pressure was greater in subjects given vasodilator-drugs versus non-vasodilators, despite similar brachial SBP[141]. The clinical implications highlighted in this work helped to substantiate findings from other studies[142-145] indicating that central blood pressure could offer a better prediction of CVD risk than peripheral blood pressure alone. Therefore, central blood pressure parameters are now often included in the study and interpretation of vessel hemodynamics and CVD risk classification[129].

2.3.4 Assessment of Arterial Stiffness

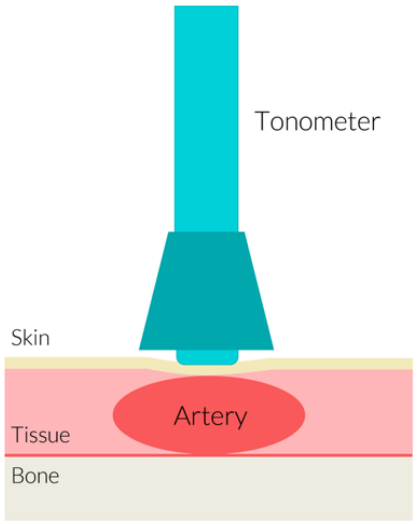
Several non-invasive measurement techniques and devices have been developed to assess arterial stiffness, including Doppler ultrasound (echo-tracking), phase-contrast magnetic resonance imaging, oscillometric pressure wave detection, and applanation tonometry[139,146,147]. The latter two techniques are more widely used as they are more practical and affordable, as well as less operator-dependent than ultrasound and magnetic resonance imaging.

2.3.4.1 Applanation Tonometry

Applanation tonometry has been widely adopted in research settings as a simple and reproducible technique that provides measurements of PWV, wave reflection, and central hemodynamics[127]. The technique applies a similar principle to what ophthalmologists use

to measure intraocular pressure. A pressure-sensing tonometer is placed on a superficial artery (typically radial, carotid, or femoral) at the point of maximum pulsation. By gently compressing the artery against an underlying structure, such as a bone, the change in pulse pressure against the artery wall is captured as a high-fidelity waveform (Figure 2.4).

Figure 2.4. Applanation Tonometry Technique



The acquired waveforms have been demonstrated to accurately correspond to invasively measured arterial pressure waveforms. The SphygmoCor system (AtCor Medical, Sydney, Australia) (used herein) uses applanation for the acquisition of arterial pressure waveforms at different arterial sites, allowing for measurement of PWV and pulse wave analysis (PWA). More recently, the SphygmoCor cardiovascular management system (CvMS) was updated to include simpler, less operator-dependent cuff-based measurements of the peripheral arterial waveforms through volumetric displacement (XCEL system). The latter system was used in the PEDAL trial, while the CvMS system was used in the SMARTER trial.

Pulse Wave Velocity

The measurement of PWV is widely accepted as the most robust non-invasive method to quantify arterial stiffness[127]. It expresses the velocity of the pressure wave traveling along an artery, where higher values of PWV indicate increased arterial stiffness. The non-invasive assessment of PWV was first performed in 1922 by Bramwell and Hill[148]. They established that in order to estimate the speed of transmission of the pulse wave one should determine the time taken by the pulse wave to travel the known length of an arterial segment. Their experiments pre-dated the use of applanation tonometry, and instead used a hot wire sphygmogram to capture the arterial waveform at different pulse points over the surface of the skin. They quantified PWV in a small group of patients and demonstrated an increase in PWV with age and disease. Technological advances have greatly improved the efficiency and practicality of the technique, but the fundamental principles have not changed.

PWV is calculated by dividing the distance between a proximal and distal superficial arterial site by the time that takes the arterial pulse to travel between those sites (pulse transit time).

$$\text{PWV (m/s)} = \frac{\text{Distance between proximal and distal arterial locations}}{\text{Pulse transit time}}$$

PWV can be calculated between a number of arterial sites, but two of the more common measurements include cfPWV, a measure of central artery stiffness, and the carotid-radial PWV (crPWV), which captures peripheral artery stiffness. Measurements of PWV can be obtained at one time with two tonometers held simultaneously at each site; however, this can be technically challenging. More commonly, recordings are completed sequentially and synchronized using the R wave of a simultaneously recorded electrocardiogram (ECG). This method is used by the SphygmoCor CvMS system and

other applanation tonometry systems (PulsePen, Cardiovascular Engineering). The newer SphygmoCor XCEL system allows for the simultaneous acquisition of the carotid and femoral pressure waveforms. A specialized cuff is placed around the thigh to facilitate the acquisition of the femoral pulse and applanation tonometry is used at the carotid site at the same time.

The distance between the two arterial sites (carotid to femoral or carotid to radial) is measured manually over the skin using a tape measure. A simple measurement of the distance between the two sites leads to an overestimation of PWV[149]. Whereas, the widely used "subtraction method" considers that in the time the pulse travels the distance between the sternal notch (closest point to the branching of the brachiocephalic artery) and the carotid artery, the pulse will have covered an equivalent distance in the aorta. Therefore, the distance from the sternal notch to the carotid site is subtracted from the sternal notch to femoral (or radial) distance. When using the XCEL device, the distance from the top of the cuff to the femoral pulse is also subtracted to adjust for the extra transit time. This subtracted distance measurement has been shown to correlate better with the true arterial path length, assessed using magnetic resonance imaging[149].

cfPWV is considered the "gold standard" measurement due to its prognostic significance. cfPWV reflects the stiffness in the arterial segment that is most susceptible to stiffening with age and cardiovascular risk factors and has been identified as an independent predictor for CVD events, as well as CVD and all-cause mortality[21,150]. The Framingham Heart Study was one of the early landmark studies to demonstrate this strong association: a 1 standard deviation (SD) increment in arterial stiffness was associated with a 48% increase in CVD risk, independently of individual vascular risk factors[21]. An extensive meta-analysis of 17 longitudinal studies (n=15,877 individuals, including healthy and higher-risk patient populations) showed that a 1 m/s increase in

aortic stiffness corresponded to a 14%, 15%, and 15% increased risk of CVD events, CVD mortality and all-cause mortality, respectively[23]. The added value of aortic stiffness in risk stratification has been highlighted in a more recent individual participant data meta-analysis (n=17,000 individuals), whereby the addition of cfPWV to a model including traditional risk factors improved classification of individual CVD risk over 10 years by 13%[3]. The prognostic significance of non-invasive arterial stiffness measurements extends to hemodialysis patients; in a cohort of 1084 hemodialysis patients, a 1 m/s increase in aortic stiffness corresponded with a 15% higher risk of non-fatal CVD events[104]. Interestingly, those with a cfPWV greater than 12 m/s had nearly double the risk of a CVD event than patients with cfPWV <8.8 m/s [HR 1.94 (95% CI 1.38, 2.72)]. Another study examining associations of cfPWV with all-cause mortality showed that a 1 m/s increase in cfPWV was associated with a 39% increased risk in all-cause mortality (adjusted relative risk 1.39, 95% CI 1.19 to 1.62, mean follow-up of 6 years)[151]. Reference values have been established in 11,092 untreated adults with no cardiovascular risk factors or disease, which enables the classification of an individual's cfPWV value as low, normal, or high for their age and blood pressure category[152]. Importantly, a cfPWV in excess of 10 m/s has been suggested to reflect hypertension-mediated organ damage[153,154]. The measurement of cfPWV has been recognized by the European Society of Hypertension guidelines[154]. An extensive and thorough scientific statement from the American Heart Association was also released in 2016 citing recommendations for the standardization of vascular research on arterial stiffness[33].

crPWV is not considered to have any prognostic significance but can provide information on the functional condition of the peripheral muscular arteries (subclavian, brachial and radial). Interestingly, crPWV has been shown to correlate well with endothelial dysfunction, as assessed by flow-mediated dilation[155,156].

Pulse Wave Analysis

Applanation tonometry enables the acquisition of a central pressure waveform and thus provides measures of central blood pressure and valuable information regarding the timing and magnitude of wave reflection. Most commonly, peripheral arterial waveforms are captured at the radial site and calibrated with brachial blood pressure[33]. A generalized transfer function is then applied to derive the corresponding central pressure waveform[157]. This indirect method has been extensively validated against intra-arterial measurement in several different patient populations[158-160]. Relevant components of the central pressure waveform include the extreme pressure points (SBP and DBP), the pulse pressure, as well as indices of wave reflection.

As previously discussed (section 2.3.3), the interaction between the forward and reflected waves generates a composite arterial pressure waveform. Measures of central pressure will depend on the timing of this interaction. Increased arterial stiffness and earlier wave reflections within the aorta increase the central pulse pressure due to an increase in central SBP and a decrease in central DBP. Therefore, central pulse pressure is often considered to be a surrogate measure of arterial stiffness[124]. A widened central pulse pressure is independently associated with a greater risk of CVD events[161]. Furthermore, central pulse pressure has been shown to be more strongly associated with carotid intima-media thickness, plaque scores, and CVD events than peripheral pulse pressure[162].

The interaction between the forward and reflected waves is marked by an 'inflection point' which can be used to define the portion of the central pulse pressure that is attributed to wave reflection[157]. The difference between the inflection point and the peak SBP is quantified as the augmentation pressure (AP). When the inflection point occurs after the peak SBP, indicating a healthy return of the reflected wave during diastole, the

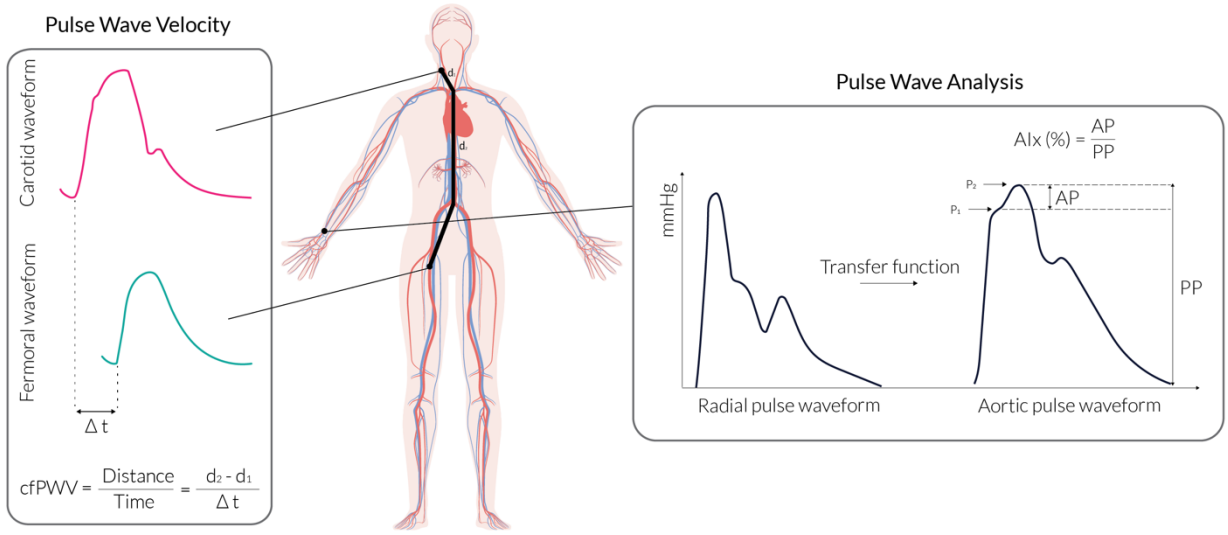
AP will be negative. However, the earlier arrival of the reflected wave generates an inflection point before the peak SBP. This adds to the SBP and leads to a positive AP. The magnitude of the AP is commonly interpreted in the context of the central pulse pressure, which is termed the augmentation index (AIx). AIx is commonly measured as an estimate of peripheral wave reflection and is calculated as follows:

$$\text{Augmentation Index (\%)} = \frac{\text{Augmentation Pressure}}{\text{Central Pulse Pressure}} \times 100$$

Since the amplitude and speed of the reflected wave are dependent upon PWV, AIx reflects to some extent the stiffness of the vasculature[163]. However, it should be acknowledged that other factors also influence AIx, including body height (aorta length and distance to reflection sites), heart rate, ejection fraction[138]. To account for the direct influence of heart rate, the SphygmoCor system provides a measure of AIx that is adjusted to a heart rate of 75 beats/min (termed AIx75)[157]. A systematic review and meta-analysis including 5,500 patients from 11 longitudinal studies demonstrated that a 10% increase in AIx was associated with a 31.8% increased risk for CVD events and a 38.4% increased risk of all-cause mortality, independently of peripheral pressures[161]. The assessment of PWA in clinical settings (including central pressures and AIx) is now reimbursable in the United States[164].

Figure 2.5 depicts the acquisition of PWA and PWV measurements using applanation tonometry.

Figure 2.5. PWV and PWA Measurements Acquired with Applanation Tonometry



2.3.4.2 Interaction Between Arterial Stiffness and Blood Pressure

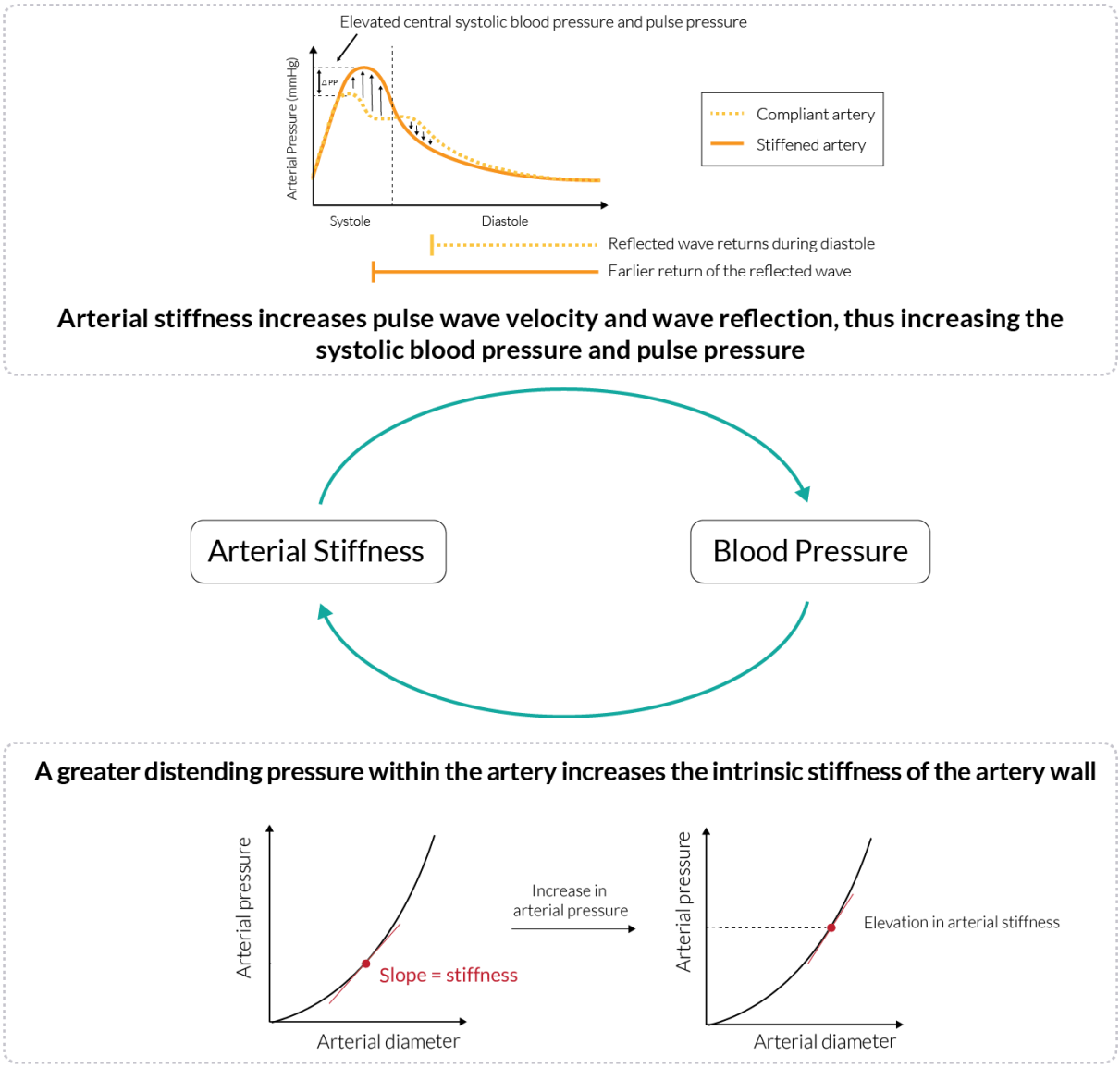
Arterial stiffening has long been implicated in the pathogenesis of hypertension; however, the direction of the relationship between arterial stiffness and elevated blood pressure has been debated, generating a chicken-or-egg conundrum[165]. Chronically elevated pressure within the artery increases aortic wall stress, which over time, accelerates the fragmentation and degradation of elastin fibers and stimulates the production of collagen[33]. The annual cfPWV progression over 6 years was shown to be greater in individuals with treated hypertension than normotensive individuals (1.5 m/s vs. 0.8 m/s per year), adjusting for age, sex and the initial cfPWV value[166]. Interestingly, the progression was steeper in individuals whose blood pressure was not controlled at follow-up than those who achieved control. Elevated SBP during childhood has also been associated with higher brachial-ankle PWV during adulthood (average of 26.5 years later)[167].

A number of studies have also indicated that elevated cfPWV may precede the development of hypertension. Associations between arterial stiffness and the future

blood pressure levels have been shown to persist when adjusting for the initial blood pressure value and other risk factors. A longitudinal analysis conducted as part of the Framingham Offspring study examined the relationship between blood pressure and cfPWV progression over 7 years in 1,759 middle-aged to older participants[168]. The initial cfPWV value was associated with the SBP 7 years later and was predictive of the development of incident hypertension. Conversely, none of the blood pressure components at baseline were significant predictors of cfPWV progression. Another study in 1,488 participants with longitudinal measurements of brachial-ankle PWV (baPWV) and blood pressure, demonstrated a significant association between baseline baPWV and SBP 4 years later, rather than the opposite direction (baseline SBP to subsequent baPWV)[169]. Altogether, these findings suggest that arterial stiffness that while arterial stiffness may precede hypertension, it is also one of its consequences.

The interdependency of blood pressure and arterial stiffness is also relevant to consider at the time the measurement is taken. As mentioned, arterial stiffness is acutely influenced by the distending pressure within the artery[170]. Conversely, the arterial stiffness influences the magnitude and timing of wave reflection, and thus will affect the shape of the pulse wave, and recorded blood pressures[171]. The bi-directional relationship is illustrated in Figure 2.6.

Figure 2.6. Bi-directional Relationship Between Arterial Stiffness and Blood Pressure



Different mechanisms for evaluating the blood pressure-independent response of arterial stiffness have been proposed. Most commonly, arterial stiffness is adjusted for blood pressure at the time of measurement. Adjusting for the mean arterial pressure (MAP) is often recommended[33,171], but it has been suggested that accounting for DBP may be more relevant as this represents the pressure in the artery when the transit time is

calculated[172]. Hermeling and colleagues have demonstrated that PWV changes dramatically over the cardiac cycle, reporting a mean difference of 2.4 m/s between the SBP and DBP (range 0.8-4.4 m/s)[173].

More recently, Spronck and colleagues introduced a new method for removing the blood pressure dependence by calculating an index of stiffness, considered equivalent to the intrinsic stiffness index β_0[172]. As previously mentioned and depicted in Figure 2.6, the intrinsic stiffness β_0 is represented by the exponent of the relationship between arterial pressure (P) and arterial diameter (D) at any given point. This relationship can be represented as follows[174]:

$$P = P_{ref} e^{\beta_0 \left(\frac{D}{Dref} - 1\right)}$$

Note: P_{ref} is a reference pressure and D_{ref} is the diameter of the artery at the reference pressure.

Spronck and colleagues derived the formula for aortic stiffness β_0 (used herein) from the formula for aortic stiffness β, described by Kawasaki and colleagues to be a blood-pressure independent measure of arterial stiffness[175]. They observed that the equation for aortic stiffness β substituted the reference pressure and diameter (P_{ref} and D_{ref}) with diastolic pressure and diameters (P_d and d_d), and thus would not accurately reflect the intrinsic stiffness β_0. Mathematically (detailed in their work[172]), they demonstrated that the aortic stiffness β differed from the true aortic stiffness β_0 by ln (P_d/P_{ref}), as shown:

$$\beta = \frac{ln\left(\frac{P_s}{P_d}\right)}{\frac{d_s}{d_d} - 1} \quad \rightarrow \quad \beta_0 = \beta - ln\left(\frac{P_d}{P_{ref}}\right)$$

To generate a measure of aortic stiffness β_0 over the length of an arterial segment (e.g., carotid-femoral), cfPWV can be integrated via the well-established Bramwell-Hill equation which describes PWV as a function of pressure and area changes[176],

$$PWV = \sqrt{\frac{1}{\rho}\frac{P_S - P_d}{A_S - A_d}A_d}$$

where ρ is the estimated blood mass density, P_S and P_d denote the systolic and diastolic pressure, and A_S and A_d denote the corresponding areas.

Therefore, using the calculated cfPWV, the corresponding DBP (P_d), as well as the estimated blood mass density as ρ =1.050 kg/L[172], aortic stiffness β_0 can be determined[172]:

$$\beta_0 = \frac{PWV^2 \cdot 2\rho}{P_d} - \ln\left(\frac{P_d}{P_{ref}}\right)$$

The assessment of aortic stiffness β_0 has shown to be valuable in studies evaluating changes in arterial stiffness when one would expect to also see blood pressure changes. For example, Desjardins and colleagues incorporated aortic stiffness β_0 into their study, which examined the reversibility of arterial stiffness after kidney transplantation[177]. Despite reductions in MAP after transplantation, they still found a reduction in aortic stiffness β_0, suggesting blood pressure-independent improvements in the intrinsic stiffness of the aorta. This was an important contribution to the field as previous studies were not able to isolate arterial stiffness from the known reduction in blood pressure with transplantation.

2.3.5 Arterial Stiffness Response to Exercise

2.3.5.1 Chronic Exercise

As previously discussed, physical activity favourably impacts CVD risk factors such as BMI, glucose, blood pressure, and lipids. However, interestingly, a significant proportion of the CVD risk reduction is independent of these factors[178] and is thought to involve improvements in arterial health[24]. In fact, even in the presence of CVD risk factors, there is some evidence in animal models to suggest that that exercise helps the

arteries build up a resistance against these harmful risk factors[61]. For example, an exercise intervention in older sedentary mice protected them from the detrimental vascular effects of high-fat Western diet[179].

A systematic review and meta-analysis of 42 studies (1,627 individuals) demonstrated that aerobic exercise interventions leads to conclusive improvements in baPWV (-1.01 m/s, 95% CI -1.57, -0.44), cfPWV (-0.39 m/s, 95% CI -0.52, -0.27) and wave reflection (-2.63%, 95% CI -5.25, -0.02)[24]. Interestingly, these effects were enhanced in participants with higher arterial stiffness (cfPWV ≥8 m/s) and influenced by the intensity and duration of the exercise intervention. Nonetheless, lower intensity forms of physical activity such as walking have also been linked with lower arterial stiffness. Baseline analyses from the SMARTER trial demonstrated a significant association between ambulatory physical activity and arterial stiffness, above and beyond traditional CVD risk factors: a 1,000-step/day increment was associated with a 0.1 m/s lower cfPWV[180]. In another study, walking habits were also shown to influence the progression of arterial stiffening; most active individuals (>10,000 steps/day) had the slowest progression of arterial stiffness over 4 years[181]. In patients with T2DM, a 1,000-step/day increment at baseline was associated with 0.1 m/s slower progression of cfPWV over 4 years[181].

These beneficial effects of physical activity are mediated through a number of different mechanisms involving both the functional and structural components of arterial stiffness. The mechanisms have largely been studied in the context of exercise interventions, but similar mechanisms are likely at play in response to unstructured forms of physical activity. Regular exercise has been shown to improve NO bioavailability, which enhances the overall vasodilatory capacity of the artery[182]. This is accomplished through increases in vascular shear and upregulation of eNOS activity in vascular endothelial cells[182].

Importantly, NO also counters the effects of the vasoconstricting peptide endothelin-1, the levels of which are elevated in the presence of hypertension, T2DM and CKD[179,183]. Exercise also has important anti-oxidant effects, thus countering the inactivation of NO by reactive oxygen species[182]. Reductions in pro-inflammatory markers, including C-reactive protein, interleukin-6 and tumour necrosis factor-α have been reported; these are markers that have been shown to reflect the functional and structural integrity of the arteries[182,184]. Structurally, exercise has been shown to mitigate the cross-linking of structural proteins by AGEs within the arterial wall and inhibits the smooth muscle-mediated synthesis of collagen, both key contributors to arterial stiffness[66].

2.3.5.2 Acute Exercise

With increased metabolic demands during acute exercise, the vascular system plays an important role in the redistribution of blood flow to ensure adequate perfusion of the exercising muscle[185]. We observe a transient increase in MAP, sympathetic activity, and vascular tone, as well as changes in arterial stiffness. I co-authored a systematic review that evaluated the impact of acute aerobic exercise on immediate changes in arterial stiffness[186]. Our results revealed that the effect of acute aerobic exercise on arterial stiffness was dependent on the time at which the measurement was performed post-exercise, as well as on the arterial segment assessed. Arterial stiffness of the central and peripheral upper body arterial segments increased relative to the resting values immediately post-exercise (0-5 minutes), and thereafter (>5 minutes) decreased to or below resting values. In the arterial segments closer to the primary working muscles (lower limbs), arterial stiffness decreased immediately post-exercise (0-5 minutes), and this reduction continued into the recovery period post-exercise (>5 minutes).

The changes in arterial stiffness with acute exercise are likely in part a function of the acute blood pressure increase. As previously discussed, as the pressure within the artery increases, the load within the arterial wall will shift from the more extensible elastin fibers to the more rigid collagen fibers, thereby increasing the overall arterial stiffness of that segment[187,188]. Other mechanisms are also likely to contribute as studies have demonstrated acute increases in arterial stiffness, independently of blood pressure[186]. This may include an acute impairment in endothelial function, vasoconstriction in response to elevated endothelin-1 levels, and increased sympathetic activation and circulating catecholemines[189,190]. On the contrary, the decreased arterial stiffness observed in the exercising limbs immediately after exercise may still reflect the vasodilatory state of the arteries feeding the exercising muscle beds. While this increase in arterial stiffness is recognized as a healthy adaptation to acute exercise, the extent of the increase may indicate differences in the ability of the arteries to respond to increased demands.

2.3.6 The 'Arterial Stress Test'

Cardiopulmonary exercise testing is a valuable tool that can provide a reliable and non-invasive assessment of the functional capacity of the cardiovascular and pulmonary systems. Importantly, it can also be used in clinical settings to identify the physiological limitations of either system by examining alterations in the normal physiological response to exercise[191]. A good example of this is the cardiac stress test, which is commonly used to assess the heart's response to an increased load during exercise, and importantly, can lead to the identification of cardiac abnormalities that were not clinically evident at rest. Similarly, assessing the ability of the arteries to respond to increased demands during acute physical stress can also capture critical information about vascular health. The Daskalopoulou Vascular Health Unit has developed the 'arterial stress test',

which involves measurements of arterial stiffness before and at several time points immediately after acute maximal exercise and into the recovery phase. The utility of the 'arterial stress test' was previously confirmed in a study at the Vascular Health Unit evaluating the impact of smoking on arterial stiffness in young otherwise healthy individuals. Despite no apparent differences at rest, young smokers' arteries had a blunted ability to respond to acute physical stress[26]. I was involved in this study during my Master's. I also identified differences in the response of endothelin-1, suggesting an altered endothelial response to exercise[192].

The 'arterial stress test' has the potential to improve our understanding of the cardiovascular response to exercise in adults with T2DM, who are known to have a greater blood pressure response to acute maximal exercise[28]. While the normal physiological response to exercise involves a significant increase in SBP, an elevation in SBP that exceeds 210 mmHg in men and 190 mmHg in women is considered to be an abnormal response[30]. Smaller changes are typically observed for DBP and an exaggerated DBP response (>110 mmHg in men and women) is less commonly observed[30]. This abnormal SBP or DBP response has been termed a hypertensive response to exercise or exaggerated exercise blood pressure, and can be unrelated to resting blood pressure levels, or whether individuals are treated with blood pressure lowering medications[30].

A hypertensive response to exercise has been associated with the future incidence of hypertension (in normotensive or pre-hypertensive individuals), as well as higher CVD risk and mortality, independently of resting blood pressure[29]. In a meta-analysis that included 12 longitudinal studies compromising 46,314 individuals with a mean follow-up of 15 years, a hypertensive response to exercise was associated with a 36% greater risk of CVD events and mortality (95% CI 1.02-1.83)[29]. They further demonstrated a 4% increase in CVD risk per 10 mmHg increase in SBP during exercise (95% CI 1.01-1.07).

These associations were independent of office blood pressure, age or CVD risk factors. Understanding the physiological changes underlying this altered response has not been fully elucidated, but vascular abnormalities are thought to play a pivotal role.

As previously discussed, T2DM leads to an accelerated stiffening of the arteries through pathological changes in the vasculature, including reduced NO bioavailability, increased oxidative stress and inflammation, as well as structural changes within the arterial wall[118]. Previous work has demonstrated that individuals with T2DM also exhibit differences in the response of central SBP[28]. However, whether individuals with T2DM have a different arterial stiffness response to maximal exercise, independent of the resting value, has yet to be explored.

CHAPTER 3: General Methodology

Methods are described in each of the manuscripts (Chapters 4-7); however, the following chapter provides a more comprehensive and detailed description of the methods used in this thesis. Statistical methods will be summarized in each of the manuscripts.

3.1 SMARTER Trial (Manuscript 1, 2, 4, 5 and 6)

3.1.1 Ethical Approval

SMARTER trial procedures were approved by McGill University's Faculty of Medicine Institutional Review Board (A08-M76-11B) and participating institutions (McGill University Health Centre, St. Mary's Hospital, Jewish General Hospital, Institut de recherches cliniques de Montréal). An amendment to conduct the qualitative study was later requested and approved.

All participants provided informed consent to participate in the SMARTER trial. Participants recruited for the qualitative study signed a separate document of informed consent. All participants gave permission to be audio taped during the interview. They also agreed to the possible inclusion of quotes from the interview in written materials resulting from the study.

3.1.2 Trial Registration

The SMARTER trial was registered on Clinicaltrials.gov on November 21, 2011 (#NCT01475201).

3.1.3 Participants

Inclusion criteria for the SMARTER trial were the following: (i) aged >18 years, (ii) baseline BMI ≥25 kg/m^2 but <40 kg/m^2; (iii) T2DM and/or hypertension; (iv) conversant in English or French; (v) did not self-report of ≥150 minutes of leisure-time physical

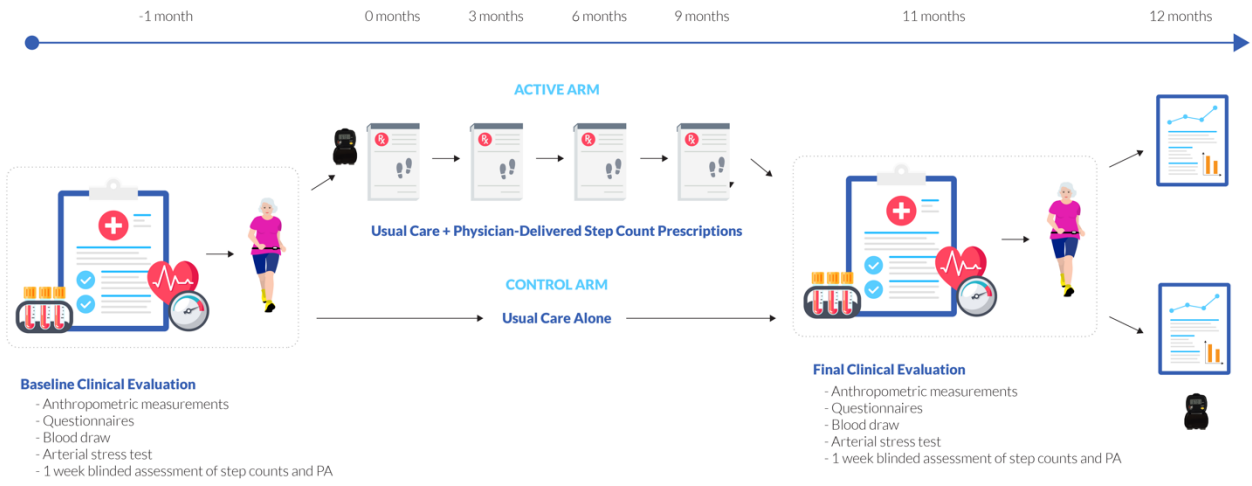
activity per week; (vi) did not have gait abnormalities that would influence their ability to walk; and (vii) were not pregnant or planning a pregnancy.

3.1.4 Trial Overview

The primary research objective of SMARTER trial was to evaluate the impact of physician-delivered step count prescriptions on arterial health, over 1-year, compared with usual care, in sedentary adults who are overweight/obese with T2DM and/or hypertension.

Clinical evaluations of cardiometabolic health were performed at baseline and then repeated after the intervention (1 year). After each evaluation, participants performed a 1-week blinded assessment of step counts and physical activity with a pedometer and accelerometer. Active arm participants received their usual care and formalized step count prescriptions at their next 3-4 regular visits with their physician (approximately every 3 months), along with a pedometer to record their daily steps. Control arm participants received usual care. After completing the final clinical evaluation, participants received a study evaluation report from their physician at the next visit. Control arm participants also received a pedometer at the end of the study. SMARTER trial procedures are outlined in Figure 3.1 and the relevant procedures for this thesis are described in detail in subsequent sections.

Figure 3.1. SMARTER trial overview



3.1.5 Quantitative Procedures

Data from the baseline clinical evaluation and step count data collected during the intervention have been used in this thesis (*Manuscripts 2, 4, 5, and 6*). The procedures were as follows:

Prior to the assessment, all participants were asked to abstain from: i) exercise for at least 24-h, ii) caffeine and alcohol intake for at least 12-h, and in the case of smokers iii) smoking for at least 12-h. It should be noted that while participants were fasted prior to the assessment, they were offered a small healthy snack after the blood test and prior to the 'arterial stress test' to prevent hypoglycemia, especially in participants with T2DM, and because a fasted state may have prevented participants from exerting themselves fully. The salt content in the snacks provided to participants was deliberately low. To avoid circadian rhythm variations, assessments were all performed in the morning in the same controlled room at the Vascular Health Unit[193,194].

Participants completed a questionnaire, including sociodemographics, past medical history, current medication use, and lifestyle habits, smoking history. Height and weight

were measured, as well as waist and hip circumferences. BMI was calculated as weight (kg) × height $(m)^{-2}$. The waist to hip ratio was calculated as waist circumference divided by the hip circumference.

3.1.5.1 Arterial Stress Test

Participants underwent the 'arterial stress test', which consists of measurements of arterial stiffness and hemodynamics at rest and at several time points after maximal exercise (3, 5, 10, 15, and 20 minutes). The 'arterial stress test' was carried out by a trained student and kinesiologist following a standardized protocol.

Exercise Test

The exercise test consisted of a supervised incremental exercise test to volitional exhaustion on a treadmill (Trackmaster, FullVision Inc., Newton, KS, USA) following the Bruce Protocol. A modified version of the protocol, which has been developed for individuals with a lower exercise tolerance was used[195]. Following a 3-minute warm-up stage, the speed and incline increased in stages of 3 minutes until participants reported reaching exhaustion.

Participants were equipped with a fitted face mask for respiratory measurements. Using indirect calorimetry, a metabolic cart (Ergocard, Medisoft, Sorinne, Belgium) was used to calculate the volume and gas concentrations of inspired and expired air during exercise. The respiratory exchange ratio (expired CO_2/expired O_2) was assessed to gauge the level of effort and the VO_2 peak was evaluated as a measure of cardiorespiratory fitness. Heart rate was monitored throughout exercise using the 3-lead ECG connected to the metabolic cart. Maximal heart rate, time to exercise completion, VO_2 peak, and maximal RER were recorded.

The maximal RER was used to determine whether participants performed a maximal exercise test. Typically, a RER > 1.1 would indicate that maximal exercise was achieved; however, this is often not achieved in older participants[196]. The decrease in RER in older subjects may be caused by a shift from type II to type I muscle fibers and greater utilization of lipids as opposed to carbohydrates for energy, thus reducing the CO_2 elimination[196]. Therefore, age-based cut-offs have been suggested and were used herein: max RER ≥1.1, ≥1.05, ≥1.0 for individuals aged 20-49, 50-65, and ≥65 years, respectively[196].

Arterial Stiffness and Hemodynamic Measurements

Participants were asked to rest without distractions (ex. cellphone) and refrain from talking or sleeping during the measurements. The following measures brachial blood pressure were obtained:

Seated: At rest (before the performance of the 'arterial stress test'), blood pressure was measured in a seated position using an automated oscillometric blood pressure monitor (BpTRU, Medical Devices Ltd, BC, Canada). The participant was left unattended to reduce the 'white coat' effect; 6 measurements of blood pressure at 1-minute intervals were obtained. To reduce the 'white coat effect', the first measure was discarded and the average of the subsequent 5 measures was reported[10]. This measure aligns with clinical guidelines for the measurement of blood pressure, which recommend the blood pressure be taken in a seated position[197].

Supine: At rest, and following exercise at 3, 5, 10, 15, and 20 minutes using an automated blood pressure monitor (BpTRU). At rest, blood pressure was measured in triplicate. The first measure was discarded, and the average of the subsequent two measures was recorded. Single measurements were accepted post-exercise due to time restrictions. Blood pressure was measured in the supine position given that

arterial stiffness measurements require adjustment for blood pressure at the time of measurement in the same position.

Standing: Immediately before and after maximal exercise (0 minutes) while standing at the treadmill blood pressure was measured using the auscultatory method. This measure was used to evaluate whether participants experienced a hypertensive response to exercise. Obtaining a value in the standing position enabled us to evaluate the change in blood pressure with acute maximal exercise (performed standing) without the influence of a postural change.

Non-invasive measurements of arterial stiffness measures, wave reflection, and central blood pressure were obtained using applanation tonometry in a supine position. The SphygmoCor CvMS system was used (AtCor Medical, Sydney, Australia) and connected to a dedicated laptop with SphygmoCor software version 9 installed. A handheld tonometer with a micromanometer tip (SPT-301, Millar Instruments, Houston, TX, USA) was gently applied perpendicularly on the skin's surface at the location of the radial, carotid and femoral pulse. A high-fidelity waveform was captured, enabling measurements of PWV and PWA.

Pulse Wave Velocity (PWV)

cfPWV and crPWV measurements were obtained as measures of arterial stiffness of the central elastic arteries and the peripheral muscular arteries, respectively. A sequence of arterial pressure waves was recorded at a proximal site (carotid artery), and a distal site (radial or femoral) within the arterial tree and synchronized using the R-wave of the electrocardiogram recordings. Due to the influence of heart rate on the timing of the pulse, measurements were only considered valid if the heart rate difference between sites was ≤ 5 bpm. An intersecting tangent algorithm was used to identify the foot of each

waveform, which is the lowest point preceding the sharp rise in pressure at the start of systole. The pulse transit time between the two recording sites was calculated using the 'foot to foot method' as the *time between the R-wave and the foot of the proximal pulse* minus the *time between R-wave and the foot of the distal pulse*. The pulse transit time was averaged across 10 seconds of recording. The pulse sites were marked with a pen to ensure consistency, and the distance between pulse sites was measured on the surface of the body using a tape measure. The distance traveled by the propagating pulse was approximated using the 'subtraction method', which subtracts the distance between the *sternal notch and the carotid site* from the distance between the *femoral site and sternal notch* (cfPWV) or the *radial site and sternal notch* (crPWV)[157]. PWV was calculated as the ratio of the transit distance and time delay between the foot of the proximal and distal waveforms (expressed as m/s).

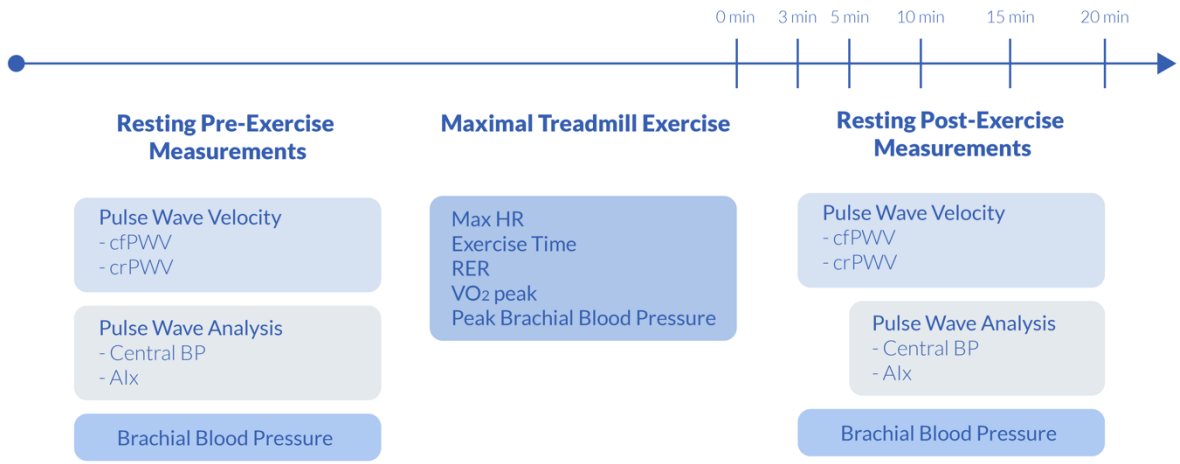
Resting measurements of crPWV and cfPWV were performed until two good quality PWV readings were within 0.5 m/s of each other. Due to time constraints post-exercise, only one reading was obtained for each measure of cfPWV and crPWV. At 3 minutes post-exercise, only cfPWV was assessed; however, both cfPWV and crPWV were assessed at all other time points post-exercise (5, 10, 15, and 20 minutes). At the same time points, brachial blood pressure was measured in the contralateral arm.

Pulse Wave Analysis (PWA)

Ten seconds of sequential waveforms were obtained at the radial pulse to generate an averaged peripheral waveform. A validated generalized transfer function was applied to derive the ascending central pressure waveform, allowing for estimates of central SBP and DBP, MAP, pulse pressure as well as indices of wave reflection (AP, AIx, and AIx75)[157]. The waveform is calibrated using brachial blood pressure. As per

recommendations by SphygmoCor, SBP and DBP values were used. However, in *Manuscript 4*, we additionally considered calibration with MAP and DBP, as this method has been increasingly suggested[198]. The quality of the collected waveforms was assessed visually by the operator, as well as the device's internal quality control system; only measurements with an operator index ≥80 were considered acceptable. Resting measurements of PWA were taken until there were two acceptable readings with values of AIx, AIx75, and AP that were within 4% of each other. Due to time constraints, single PWA measurements were performed post-exercise at 5, 10, 15, and 20 minutes. Figure 3.2 summarizes the 'arterial stress test' procedure.

Figure 3.2. Arterial Stress Test Measurement Time Points



Validity and Reproducibility of SphygmoCor Measurements

As previously mentioned, the validity of the SphygmoCor generalized transfer function has been confirmed by direct arterial measurements obtained via catheterization[158-160]. Furthermore, good inter- and intra-observer reproducibility and repeatability have been demonstrated for PWV and PWA indices among various populations, including individuals with hypertension, T2DM and CKD[199-202]. All

operators at the VHU underwent extensive training on applanation tonometry; but there is evidence to suggest that PWA measurements are reproducible even when inexperienced operators performed the test[202].

Measurements of PWV and PWA using the SphygmoCor device have also been validated for use during and after exercise. For example, Sharman and colleagues showed that non-invasively recorded central waveforms (derived from the radial artery) were comparable with invasively recorded central waveforms at rest, as well as during and after supine cycling exercise in patients undergoing diagnostic coronary angiography[203]. A study by Holland and colleagues demonstrated good reproducibility of central blood pressure and AIx between two visits in which measurements were performed at rest, during submaximal cycling exercise, and immediately after maximal treadmill exercise (intraclass correlation coefficient >80 for all)[204]. Similarly, good test-retest reproducibility over 2 separate visits has been demonstrated for cfPWV measured immediately after stopping light-moderate cycling exercise (mean difference 0.35 ± 0.61 m/s, intraclass correlation coefficient of 0.87)[205]. Therefore, in spite of significant exercise-induced increases in blood pressure and heart rate, these findings support using applanation tonometry to collect reliable measures of central hemodynamics and arterial stiffness during, as well as immediately after exercise.

3.1.5.2 Baseline Assessment of Step Counts and Physical Activity

Participants were provided with a concealed Yamax SW-200 pedometer (StepsCount, Ontario, Canada) and an ActiGraph GT3X+ accelerometer (ActiGraph Corp., Pensacola, FL, USA), both to be worn for 1-week for the quantification of average daily steps, as well as duration, frequency, and intensity of physical activity.

The Yamax SW-200 pedometer has a coiled spring-suspended lever arm requiring 0.35g of vertical acceleration and was worn at the waist in all participants during waking hours. Participants were provided with a stamped, pre-addressed envelope that included a second pedometer to record the "false steps" that occurred during the mailing process.

The ActiGraph GT3X+ is a capacitive accelerometer, whereby acceleration is calculated from changes in capacitance of the sensing element. Unlike the pedometer, which only captures movement in the vertical direction, the accelerometer captures the acceleration along 3 axes: vertical, anteroposterior, and mediolateral. The accelerometer was worn at the waist in the majority of participants; however, a subset of participants wore the accelerometer on the non-dominant wrist (n=46). Analyses were conducted in participants who wore the accelerometer for ≥10 hours/day for at least 4 out of the 7 days to ensure accurate assessments. Non-wear time was defined as 60 consecutive minutes of zero activity counts, and the spike tolerance was set to 2 minutes of >100 activity counts. The well-validated Freedson adult 1998 energy estimation equation was applied[206], and physical activity levels were classified using cut-points previously used in a similar population of older sedentary adults (sedentary: <200 counts/min, light: 200-1,999 counts/min, moderate: 2,000-3,999 counts/min, vigorous: ≥4,000 counts per min)[207]. The data were processed in 10-second epochs using the ActiLife software version 6.5.4.

3.1.5.3 Daily Step Counts

During the SMARTER intervention, participants in the active arm were provided with a pedometer and instructed to wear it each day and record their step counts in the step count log book provided to them. Participants received step count prescriptions from their treating physician at clinic visits every 3-4 months (*Appendix B*). The prescriptions were tailored to the baseline activity levels, with a slower rate of increase in more

sedentary participants (*Appendix C*). For all participants, the overall goal was a net increase of 3,000 steps / day over 1 year. Step log books were returned to the research team after completing the intervention. Daily step counts for participants were extracted manually from the log books.

3.1.6 Qualitative Procedures

3.1.6.1 Participants and Sampling Strategies

A qualitative description study was conducted in a subset of SMARTER active arm participants and collaborating physicians to explore individual experiences of participants and collaborating physicians' involvement with the SMARTER trial. Among SMARTER active arm participants, we conducted purposive sampling to ensure 1) maximum variation of characteristics likely to affect walking levels, including age[75] and sex[83], and included both 'successful' and 'less successful' participants in terms of step count improvement. Among SMARTER collaborating physicians who followed at least 1 active and 1 control arm participant, we conducted purposive sampling to ensure inclusion of physicians who had recruited both high and low numbers of participants, equal sex representation, and maximum variation in the number of years in practice.

3.1.6.2 Interviews

Semi-structured individual interviews were conducted in person with collaborating physicians and over the phone with SMARTER participants. Individual interviews were selected over focus groups since they allowed for a more in-depth exploration of individual experiences with the intervention. Furthermore, individual interviews accommodated the very busy schedules of physicians better than focus groups. Interviews were conducted over the phone with participants for practical reasons. While this is sometimes considered a less attractive alternative to in-person interviews, studies

have shown no differences in the quality of the interview[208]. Furthermore, non-verbal data (body language, visual cues, etc.) was not considered relevant in our study.

The interviews were conducted using interview guides (*Appendix D*), which were specifically oriented for each group (active arm participants and collaborating physicians). Together, the guides were designed to assess a) overall acceptability of the SMARTER strategy, b) perceived values and benefits of the strategy, c) facilitators and barriers associated with the implementation of such a strategy, and d) feasibility for widespread clinical implementation. All interviews were audio-recorded using two digital voice recorders and transcribed verbatim immediately afterward.

3.1.6.3 Methods for Analyzing Data

Thematic analysis of the interviews was performed using methods elaborated by Braun and Clarke[209]. Thematic analysis is a widely used analytical approach in applied health research and recognized for its accessibility, robustness, and flexibility within different theoretical frameworks[209,210].

Dr. Romina Pace, a member of Dr. Dasgupta's research team, and I were responsible for conducting the thematic analysis. All transcripts were read, re-read, and responses were independently coded to catalogue emerging themes and sub-themes. To determine proper code assignment, each coder compared specific text segments with other segments that have previously been assigned the same code to ensure they reflect a similar concept. Any differences in coding were discussed until a consensus was reached. Data coding and organization were facilitated by Dedoose, a widely used content analysis software (Dedoose v.7.0.23, SocioCultural Research Consultants, Los Angeles, CA).

Codes were organized into sub-themes and overall themes, which were discussed with SMARTER investigators (K. Dasgupta and SS. Daskalopoulou). Themes that were reported by over half of the participants in each group were reported.

3.1.6.4 Theoretical Framework

As we explored the experiences and views of participants undergoing the intervention, we took into consideration various known beliefs that have been shown to influence health-related behavior change. We incorporated the Theory of Planned Behavior by Fishbein and Ajzen[211], which is recognized as a relevant theoretical model for evaluating health-related behavior change interventions, including those involving walking[212-215]. The theory focuses on the intention-behavior relationship and suggests that a person's ultimate behavior is dependent on their intention to engage in that behavior, or in the context of our study, their intention to increase walking levels. A person's level of intent would be shaped by their a) *attitude toward the behavior*, for example, if they believe that adhering to the step counts will benefit them; b) *subjective norms*, which refers to a their perception about what others around them want them to do and their motivation to meet their expectations, which in our study, includes physician; and c) *perceived behavioral control* or the belief that they have the skills, ability, willpower, time, and support to increase the amount they walk[211]. Therefore, understanding how the strategy has impacted participant's beliefs, and ultimately their intention and behavior to walk more, were relevant to understanding the strategy's strengths and weaknesses, as well as areas for improvement. Moreover, consciously developing the intention may not be sufficient to change behavior, as unconscious processes may also be at play. Through the lens of the Dual Process Theory, we also considered habit, which has been

recognized as an important driver for sustainable behavior change involving physical activity[216,217].

To elaborate on physicians' responses to the intervention and willingness to adopt the strategy, we used Roger's diffusion of innovation theory[218]. We identified specific challenges associated with the adoption and sustainability of the strategy by specifically exploring Rogers' five process factors, which include: a) the *relative advantage,* or the degree to which the strategy is perceived better than other exercise promotion strategies or current practice; b) *compatibility*, or the degree to which the strategy is perceived as being consistent with the existing values, and the needs of both patients and physicians; c) *complexity,* or the perceived difficulty of adopting the strategy; d) *trialability*, or the degree to which the strategy can be experimented with in the absence of considerable resources, and lastly, e) *observability*, or how visible the strategy is to others[218]. The diffusion of innovation theory has been widely applied in clinical practice to understand better challenges associated with the diffusion and adoption of new technologies and practices, including health promotion strategies[219-222].

3.1.6.5 Methods for Ensuring Rigor and Trustworthiness

We applied several techniques to ensure methodological rigor and trustworthiness[223]. Throughout the analysis process, we used independent coding by two members of the research team, comparison of results, and peer examination with SMARTER investigators to establish credibility. In reporting the results of this study, we were transparent in our description of the study context to enhance the transferability of our results to other patient groups, settings, or exercise promotion strategies. Moreover, in order to ensure dependability and confirmability, we clearly documented the various processes and methodological considerations so that other researchers in the field will be able to

evaluate the integrity of our conclusions. Our choice of a qualitative description research design puts a greater emphasis on providing near-data interpretations of the interview content, thus minimizing the risk of misinterpretation.

3.2 PEDAL Trial (Manuscript 3)

3.2.1 Ethical Approval

The trial was approved as a pilot project by the McGill University Health Centre (MUHC) ethics board and written informed consent was obtained from all participants.

3.2.2 Trial Registration

The trial was registered on clinicaltrials.org on January 23, 2017 (#NCT03027778)

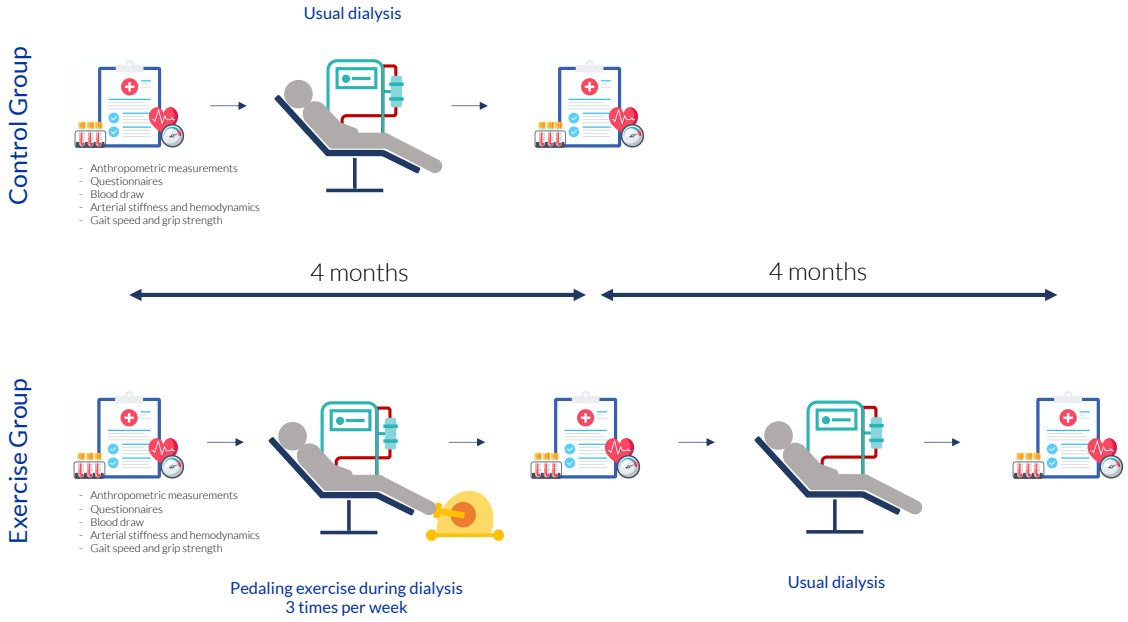
3.2.3 Trial Overview

The main objective of the PEDAL pilot trial was to evaluate: 1) the effect of intradialytic pedaling exercise on arterial stiffness and hemodynamic parameters over 4 months, compared with usual dialysis, and 2) the longer-term effect of pedaling on arterial stiffness and hemodynamic parameters 4 months after completing the 4-month exercise intervention (8 months after trial initiation). The trial also aimed to examine the impact of intradialytic pedaling exercise, compared with usual care, on general health, anthropometric measures, physical function, and routine laboratory blood markers as secondary outcome measures, as well as to assess feasibility, safety and adverse events associated with the intradialytic pedalling exercise.

It should be noted that this trial was initially designed as a randomized controlled cross-over trial; however, the trial time frame had to be shortened due to a hospital-wide move and the closing of the dialysis unit at the Royal Victoria Hospital (one of the 2 sites).

Patients were relocated to various other sites, which required us to complete the trial before the move. As a result, we were not able to include an adequate wash-out period and opted to carry out the trial as a 4-month randomized controlled trial with 4-month follow-up post-exercise cessation (Figure 3.3).

Figure 3.3 PEDAL Trial Overview



3.2.4 Participants

We recruited adults over the age of 18 years old with ESRD, who were on a stable in-center hemodialysis regimen (approximately 4 hours 3 times per week) for ≥ 12 weeks prior to recruitment. A cardiac evaluation was required within the last year to ensure adequate cardiac function to undergo the exercise program.

Exclusion criteria were 1) any physical or psychological disability that would impact trial participation 2) serum intact parathyroid hormone >250 pmol/L within 30 days prior to screening visit, 3) dysrhythmia or severe cardiac disease, such as congestive heart failure Class III-IV, or unstable CVD within 90 days prior to recruitment, 4) severe peripheral arterial disease, 5) severe hyperkalemia (>6.5 mmol/L) consistently for the last

2 weeks, 6) current active cancer (excluding basal cell carcinoma of the skin), 5) poorly controlled hypertension (post-dialytic SBP ≥160mmHg or DBP ≥100mmHg) within 4 weeks prior to recruitment, 6) anticipated living donor kidney transplant or any other planned major surgery over the trial duration, or 7) history of poor treatment adherence.

3.2.5 Procedures

3.2.5.1 Arterial Stiffness and Hemodynamics

Arterial stiffness and hemodynamic parameters were measured non-invasively using applanation tonometry. Unlike the SMARTER trial in which the SphygmoCor CVMS device was used, the PEDAL trial used the SphygmoCor XCEL device (AtCor Medical, Sydney, Australia), a newer model that incorporates cuff-based measurements to simplify the procedure. The same protocol was followed between the two devices; however, the following differences should be noted. Firstly, assessments were conducted in a semi-supine position (20% inclination) as the beds in the dialysis unit could not be lowered further. Second, brachial blood pressure was measured directly using the automated blood pressure cuff attached to the XCEL device. The cuff then partially re-inflated to sub-DBP to measure the pressure oscillations and calculate an averaged brachial waveform. A validated generalized transfer function was applied to generate the central pressure waveform. Third, measurements of cfPWV were performed using a thigh cuff and carotid tonometry. The distance between the carotid and femoral location was measured over the surface of the skin with a tape measure. Participants were asked to refrain from caffeine, alcohol, and smoking at least 5 hours before the assessment, and assessments before and after the intervention were conducted at the same time for each participant (prior to starting the mid-week dialysis session).

3.2.5.2 Physical Functioning

Gait speed was measured with a timer (in seconds) as the participant was asked to walk a 6-meter course as quickly as possible. Two readings were taken, and the average was recorded. Grip strength was measured using a hand dynamometer (Lafayette Instrument, Lafayette, IN, USA) in both the dominant and non-dominant hand. Two readings were recorded in each hand, and the highest measure was reported. All participants completed the short form of the International Physical Activity Questionnaire (IPAQ) to assess baseline physical activity levels[224].

3.2.5.3 Blood Collection

Blood samples were collected at baseline and final assessments for the assessment of the following: hemoglobin, leukocytes, platelets, serum albumin, serum electrolytes, total calcium, phosphate, parathyroid hormone levels, total cholesterol, triglycerides, high-density lipoprotein cholesterol, iron studies, and ferritin. Low-density lipoprotein calculated using the Friedewald formula[225]. Furthermore, single pool Kt/V was measured to quantify hemodialysis treatment efficacy. Blood analyses were performed at the Central Laboratories of the MUHC using standard methods.

3.2.5.4 Randomization

Eligible participants were allocated to the exercise or control group by stratified permuted block randomization. Factors for stratification included age and sex.

3.2.5.5 Exercise Protocol

Participants in the exercise group performed pedaling exercise 3 times/week during the first 2 hours of dialysis for 4 months. Blood pressure and heart rate were monitored during exercise, and exercise time was recorded after each session. Participants in the exercise group exercised for the amount of time that allowed them to reach the target

range of 12-16 out of 20 points ("somewhat hard" to "hard") on the Borg Rating of Perceived Exertion Scale[226]. As advised by the nephrologist, patients did not exercise past the halfway mark of their dialysis session (maximum 2 hours). Exercise compliance for each participant was calculated as the number of dialysis sessions where pedaling exercise was performed divided by the total number of sessions over 4 months (48 sessions). Reasons for non-compliance were recorded.

3.3 Other Vascular Health Unit Studies (Manuscript 6)

3.3.1 Ethical Approval

Data for our analysis comparing different approaches for cfPWV measurement had been previously collected for five studies, for which ethical approval had been obtained by either the MUHC Research Ethics Board, the McGill University's Faculty of Medicine Institutional Review Board, or the Concordia University Research Ethics Board. We further obtained ethical approval for the secondary analyses (#2020-5862).

3.3.2 Participants

The study population consisted of participants recruited to participate in five existing studies at the Vascular Health Unit, including young, healthy individuals [Quantification of the effect of SMOKing on artEriaL stiffnESS (SMOKELESS), Study A], overweight/obese young, healthy individuals [Acute and Chronic Effects of Obesity (ACEO), Study B], women with high-risk singleton pregnancies assessed during the first trimester [The pRedictivE Value of artErial stiffness in pre-eclAmpsia deveLopment (REVEAL), Study C], middle-aged healthy post-menopausal women [The Effect of Dietary Calcium Intake as Compared to Calcium Supplementation on Vascular and Bone Health in Postmenopausal Women (CALCIUM), Study D], and adults who are

overweight/obese with T2DM and/or hypertension [Step Monitoring to improve ARTERial health (SMARTER), Study E]. Participants with an arrhythmia were ineligible for all studies.

3.3.3 Procedures

Measurements of cfPWV were performed non-invasively using applanation tonometry in a supine position in all studies using the SphygmoCor CVMS device (SphygmoCor, AtCor Medical, Sydney, Australia). The same protocol for resting measurements of PWA and PWV, as described in section 3.1.5.1, was followed in all studies. Raw PWV exports from each of the study databases were imported into SAS statistical program, and code was developed to remove all poor-quality measurements (overall pulse transit time variation >10%, proximal or distal site SD >6% , and heart rate difference >5 bpm). The analysis aimed to compare the median cfPWV value with 1) average of the first 2 cfPWV measures and 2) average of the 2 cfPWV measures within 0.5 m/s. Therefore, I selected participants who had 3 or more good quality cfPWV values, which was required for the calculation of a median value. Participants who did not have 2 cfPWV measures within 0.5 m/s were excluded. In studies with multiple visits, only the first visit was included.

Blood pressure was measured in a supine position, either using an automated oscillometric blood pressure monitor (BpTRU, Medical Devices Ltd, BC, Canada) (Study B, D, E) or manually using the auscultatory method (Study A and C). Three measures were taken in all participants. The first reading was discarded, and the two subsequent readings were averaged.

Sociodemographic information, smoking history, past medical history, and medication use was obtained from all participants using a questionnaire. In studies C and

E, past medication history and medication use were confirmed by the participant's treating physician.

CHAPTER 4:

Evaluation of a Step-count Prescription Physical Activity Promotion Strategy

This chapter encompasses two studies that contributed to our evaluation of a step-count prescription physical activity promotion strategy integrated into clinical practice (SMARTER trial).

4.1 Preamble – Manuscript 1

The integration of pedometers into clinical practice has the potential to enhance physical activity levels in patients with chronic disease. Our SMARTER randomized controlled trial demonstrated that a physician-delivered step count prescription strategy has measurable effects on daily steps and metabolic health[15]. As we consider the more widespread implementation of the strategy into clinical practice, I was interested in exploring in greater depth some of the factors that may have influenced participant's responsiveness to the strategy. This led me to carry out a qualitative study to identify facilitators of and barriers to the successful uptake of the strategy according to the experiences and views of trial participants undergoing the intervention as well as collaborating physicians. This work was published in March 2018 in *Diabetes Research and Clinical Practice*.

4.2 Content – Manuscript 1

A Qualitative Evaluation of a Physician-Delivered Pedometer-Based Step Count Prescription Strategy with Insight from Participants and Treating Physicians

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4.2.1 Abstract

Aims: The integration of pedometers into clinical practice has the potential to enhance physical activity levels in patients with chronic disease. Our SMARTER randomized controlled trial demonstrated that a physician-delivered step count prescription strategy has measurable effects on daily steps, glycemic control, and insulin resistance in patients with type 2 diabetes and/or hypertension. In this study, we aimed to understand perceived barriers and facilitators influencing successful uptake and sustainability of the strategy, from patient and physician perspectives.

Methods: Qualitative in-depth interviews were conducted in a purposive sample of physicians (n=10) and participants (n=30), including successful and less successful cases in terms of pedometer-assessed step count improvements. Themes that achieved saturation in either group through thematic analysis are presented.

Results: All participants appreciated the pedometer-based monitoring combined with step count prescriptions. Accountability to physicians and support offered by the trial

coordinator influenced participant motivation. Those who increased step counts adopted strategies to integrate more steps into their routines and were able to overcome weather-related barriers by finding indoor alternative options to outdoor steps. Those who decreased step counts reported difficulty in overcoming weather-related challenges, health limitations and work constraints. Physicians indicated the strategy provided a framework for discussing physical activity and motivating patients but emphasized the need for support from allied professionals to help deliver the strategy in busy clinical settings.

Conclusion: A physician-delivered step count prescription strategy was feasibly integrated into clinical practice and successful in engaging most patients; however, continual support is needed for maximal engagement and sustained use.

4.2.2. Introduction

Wearable step counting devices are popular in the general population but underused in sedentary clinical populations. Integration into clinical practice has the potential to enhance physical activity levels. In prediabetes, a 2,000 steps/day increase over 1 year was associated with an 8% reduction in cardiovascular event rates over 6 years[1]. Group-based programs integrating step counters lead to similar step increases in type 2 diabetes (T2DM), with even greater improvements when step goals were established[2]. However, increases are not sustained when the programs end.

We designed and conducted a physician-delivered step count prescription strategy versus usual care in patients with T2DM and/or hypertension (Step Monitoring to improve ARTERial health (SMARTER) randomized controlled trial), capitalizing on the fact that routine medical visits recur over time in chronic disease[3,4]. We provided

participants with simple, low-cost pedometers to wear daily. Prescriptions with individualized daily step targets, gradually increasing over a 1-year period, were provided by the treating physician at each clinical visit. Compared to control arm participants, daily step counts increased by 1,200 steps in the active arm, with improvements in glycemic control (0.38% hemoglobin A1C reduction in T2DM).

Given the benefits of the SMARTER strategy, we conducted a qualitative descriptive study herein to assess participants' and physicians' experiences and impressions of the intervention, in order to understand the perceived barriers and facilitators aiming to move towards widespread implementation.

4.2.3 Methods

SMARTER Trial Intervention

As previously reported[3,4], SMARTER included adults with T2DM and/or hypertension, excess weight, and <10,000 steps/day as measured with 1-week pedometer data (viewing window concealed). Records of active arm participants step logbooks were reviewed with their physicians at each visit (every 3-4 months), goals were established, and a written step count prescription was provided. The overall aim was a net increase of 3,000 steps/day over baseline by 1 year, with slower rates of increase at lower baseline levels. A SMARTER coordinator reminded physicians of upcoming visits with participants in-person or by phone and showed participants how to use the pedometer and record their steps.

Research Design

We conducted a qualitative descriptive study[5], to explore individual experiences (active arm SMARTER participants and collaborating physicians) at a semantic level.

Participants and Sampling Strategies

The trial and qualitative study were approved by McGill University's Faculty of Medicine Institutional Review Board and conformed to the standards set by the Declaration of Helsinki[6]. Informed consent was obtained from all participants. In order to capture a wide range of experiences and impressions of the intervention, we conducted maximum variation sampling, a commonly used purposive sampling technique in qualitative research[7].

Participants

Among the active arm participants who completed the final evaluation, we sampled both 'successful' (n=20) and 'unsuccessful' participants (n=10) in terms of step count improvements, in a similar proportion to what we observed in the full group of active arm participants wherein 36% of participants did not increase step counts. We also aimed to include a range of age groups and representation of both women and men.

Physicians

Among collaborating physicians, 62% (46/74) followed at least 1 active and 1 control arm participant. We interviewed 10 of these physicians, sampling to ensure equal sex representation, variation in years of practice, and balance between higher and lower recruiters.

Interview Methods

Guided by a semi-structured interview guide (Table 1), individual interviews were conducted (ABC) with participants (phone) and physicians (in-person). On average, participants were interviewed 14 (standard deviation, SD 4) months after final evaluations to assess sustainability. All interviews were audio recorded and transcribed verbatim. French interviews were translated to English.

Table 1. Outline of Interview Guide

SMARTER Participants
Can you describe the program and what it was like for you? *Probes: likes/dislikes, challenges, pedometer/log book use, meeting targets, walking vs. other PA, weather, health changes*
What helped you follow the program? *Probes: involvement of family, friends and peers, SMARTER coordinator, physician*
Tell me about your physical activity since the program? *Probes: continuation of pedometer use, goal setting*
SMARTER Physicians
Tell me about your experience with your patients in the intervention arm of the step count study. *Probes: likes/dislikes, challenges, pedometer/log book use, meeting targets, impact on motivation compared to usual care, barriers for implementation*
Tell me about your experience implementing the step count prescription strategy in your clinic. *Probes: impact on time/frequency of visits, involvement of SMARTER coordinator*
Tell me about your practice with your patients since the study and any improvements that you think can be made in the future. *Probes: continuation of prescription, involvement of control arm subjects or other patients, nurse vs. physician*

Full version included in Appendix D.

Analysis

Thematic analysis was performed by two trained investigators (ABC and RP)[8]. Transcripts were independently coded to determine emerging themes and sub-themes. To determine code assignment, each coder compared text segments with other segments previously been assigned the same code to ensure they reflected a similar concept. Coders continually refined the existing codes and identified new codes. Discrepancies were discussed until consensus was reached, with involvement of co-senior authors when necessary. Data coding/organization was facilitated by Dedoose v.7.0.23 (SocioCultural

Research Consultants, Los Angeles, CA). Final themes and sub-themes were discussed among all investigators. We considered saturation of sub-themes separately for those who increased step counts and those who decreased, and report herein themes that were reported by over half of the participants in each group (participants who increased, participants who decreased, and physicians).

4.2.4 Results

For a final sample of 30 participants (Table 2), a total of 40 participants were contacted; 7 could not be reached and 3 declined. All 10 physicians contacted agreed to be interviewed (Table 3). Interviews were conducted in November and December 2016 and averaged 15 (SD 4) minutes in duration for participants and 17 (SD 5) minutes for physicians.

Considerable overlap was found between participant and physician perspectives. Therefore, the results from both groups have been organized into 5 main themes (Table 4), each supported by sub-themes, presented separately for physicians and participants, and illustrated with direct quotations.

Table 2. Characteristics of Interviewed Participants and SMARTER Active Arm Completers

Participant Characteristics	Interviewed Participants (n=30)	Full group of SMARTER Active Arm Completers (n=134)
Age (years), mean (SD)	59.6 (10.4)	60.1 (10.8)
35-49, n (%)	5 (17%)	23 (17%)
50-64, n (%)	15 (50%)	61 (45%)
>65, n (%)	10 (33%)	50 (37%)
Body mass index (kg/m²), mean (SD)	31.8 (4.6)	31.5 (4.6)
Sex, n (%)		
Women	14 (47%)	71 (53%)
Men	16 (53%)	63 (47%)
HTN and/or T2DM Status, n (%)		
T2DM	19 (63%)	79 (59%)
HTN	26 (87%)	125 (93%)
Both T2DM and HTN	15 (50%)	70 (52%)
Baseline steps/day, mean (SD)	4701 (2362)	4612 (2167)
Change in steps/day from baseline n(%), mean(SD		
Decrease	10 (33%), -1056 (1037)	48 (36%), -1504 (1488)
Increase	20 (67%), 3221 (1321)	86 (64%), 2745 (1984)

HTN, hypertension; SD, standard deviation; T2DM, type 2 diabetes mellitus

Table 3. Characteristics of Interviewed SMARTER Collaborating Physicians

Physician Characteristics	N (%) or mean (SD)
Sex	
Women	5 (50%)
Men	5 (50%)
Medical Specialization	
Family Medicine	3 (30%)
Specialists	7 (70%)
Number of Years in Practice	32.9 (11.3)
<30 years	3 (30%)
30-39 years	4 (40%)
>40 years	3 (30%)
Number of Active Arm Participants	6 (3)
≤ 3 patients	3 (30%)
4-6 patients	4 (40%)
≥ 7 patients	3 (30%)

Table 4: Summary of Main Themes and Associated Sub-themes among Participant and Physicians

MAIN THEMES	Participant Sub-themes	Physician Sub-themes
Theme 1: **Effective Intervention Elements**	Positive experience with program Program was easy to understand Regular monitoring (pedometer/log book) and fixing targets (prescriptions) improved motivation Walking easier than other forms of physical activity	Positive experience applying strategy Strategy was easy to understand and apply Relative advantage: more beneficial impact on patient motivation than usual advice Provided a framework for physical activity discussion
Theme 2: **Accountability and Support**	Encouraged by physician/study coordinator Supported by family, friends, and peers	Need for external support (reliance on study coordinator)
Theme 3: **Ease of Integration**	Integrated walking into daily life Changing habits/adapting routine	Compatible with practice/structure of care No impact on frequency of visits
Theme 4: **Barriers to Uptake**	Poor weather Work constraints Physical health limitations Pedometer issues	Patients with pre-existing conditions, age of patients, physical limitations Challenges of behavior change
Theme 5: **Implementation and Sustainability**	Continued use of pedometer or other tracker, maintaining routine Health feedback: health or physical improvements during intervention as motivation Post study derailment: lack of support, discontinuation of physician prescription	Post study discontinuation of prescription: lack of support and time, extra task Supportive of future integration in clinical practice Encouraged involvement of other allied health professionals (nurses, kinesiologists) can be involved

Theme 1: Effective Intervention Elements

Participants and physicians reported positive views about the intervention (i.e., pedometer, step count prescription, log book) (Sub-theme (ST) 1.1, 1.5), describing it as easy to understand, and apply (ST 1.2, 1.6).

Irrespective of step count changes, participants reported higher motivation to be physically active with the intervention (ST 1.3). Wearing a pedometer daily provided constant feedback [*I don't have a car so I do a lot of walking, but apparently I wasn't walking what an average person does each day]* and improved self-awareness, signalling, for example, low steps, [… *I am more conscious of how much I walk, and when I don't walk enough I'm more conscious that I should put some more steps into my day].* Participants with increased counts highlighted the importance of a step count goal [*Certainly the pedometer is one thing, but also to have a goal to reach a certain number of steps was motivating*] and the consistency it promoted [*...motivated me to be more constant, to really every day do it, I was doing it before, but it wasn't as constant, there were days when I did more, or less.*]

The majority expressed a preference for walking over other forms of activity (ST 1.4) [*...walking is the easiest and the most likely for me to be involved in*]. The intervention improved motivation and confidence in ability to be active [*That one year inspired me that I could do that, and I decided at the end of the program that I would try to continue*].

Physicians agreed that the intervention structure conferred a relative advantage compared to their usual physical activity advice (ST 1.7) [*For sure, because it's kind of like they hear it (i.e., usual advice) in one ear, and it goes out the other.*] Increased motivation of patients led physicians to recruit more patients [*This is why I kept referring patients. I noticed that they were more motivated*]. They also appreciated the fact that the intervention structured physical activity discussions, providing a concrete means to encourage physical activity engagement (ST 1.8) [*It was done in a very reasonable step-by-step fashion*

that they were able to accomplish, rather than saying you've got to go from here to here which would have been impossible, so I think the mechanism was very valuable].

Theme 2: Accountability and Support

Accountability to physicians and the study greatly influenced participants' motivation to be more active (ST 2.1) [*Like anything, if you have to give your results to someone you are going to try a little harder*], [*Well it definitely got me out walking. ... I felt pressured you know, to fulfill the obligation of the program*]. Participants also appreciated the SMARTER coordinator's support [*It was nice having her in the background pushing me a little bit*]. The majority who increased step counts mentioned being encouraged by others (family, friends, and peers); participants whose step counts decreased did not report this same level of support (ST 2.2) [(Did others encourage you to walk?) *No not really, and I think that's part of the problem*].

Physicians also highlighted the SMARTER coordinator's support (ST 2.3). Some physicians felt it would be difficult to manage completely on their own [*Having (trial coordinator) coming in person was a big bonus. In a busy clinical setting I wouldn't be able to take up to half an hour explaining everything, and displaying it to my patient*], and some became reliant on this support [*Most physicians, and I include myself, wouldn't have the time to go through and look at the steps, so I think is a valuable tool that we able to use with the help of someone to do it*].

Theme 3: Ease of Integration

The majority of participants developed various strategies to increase walking levels (ST 3.1), especially, those who increased step counts. For many this involved incorporating a new routine or habit into daily life (ST 3.2) [*It would push me to go out at lunch time to take a good walk, otherwise I'd just sit and do nothing*] AND [*Instead of taking the bus for example to reach the metro, I walk to the metro. Sometimes I exit 2 stops earlier*]. For

some, these efforts led to sustainable changes [*I used to use the car to do everything; now I walk to the grocery store by foot*].

Physicians indicated the intervention to be compatible with their practice and structure of care (ST 3.3) and without impact on the time or frequency of visits (ST 3.4) [*These patients I was seeing for other reasons anyways*]. However, many relied on study coordinator support, as discussed above (Theme 2).

Theme 4: Barriers to Uptake

Participants acknowledged weather-related barriers (ST 4.1) [*I certainly walked a lot less in the winter. It was really, really cold*]. Work constraints (ST 4.2) [*The biggest challenge for me are my work hours. Making the time for it, but also trying to fit it in to a time of day that is normal for people. Also, I work from home, I don't even get that morning walk getting to the bus or the metro and getting to work, so it's really challenging*] and health limitations that emerged during the trial period were cited as a significant barrier in participants who were not able to increase their step counts (ST 4.3) [*I have two herniated disks. So there were several times where it was impossible for me to do all the steps because I was not mobile*]

More successful participants developed strategies to overcome barriers, [*In the snow, I do a little more elliptical to compensate or I go to the shopping center to walk*], while those who decreased were unable to overcome barriers [*... you are at work all day, and by the time you get home, I mean there is only so much you can do, you know. By the time you sit its 10 o'clock, I'm definitely not going jogging... There are other responsibilities in life…*]. Some participants raised concerns about the accuracy of the pedometer (ST 4.4), [*I didn't find it a very good one. It would either not do your steps or it would count too much, it wasn't accurate*] or found the waist placement was not suitable with certain outfits [*If I was wearing a dress for occasions then those were the days I would skip wearing it*]. However, this seemed to be only

a minor hindrance as most participants citing issues with the pedometer in fact increased their step counts in response to the intervention.

Physicians echoed similar sub-themes, particularly the challenge of applying the strategy with participants who developed physical impairments or other co-morbidities over the course of the intervention (ST 4.5) [*They actually did comply, came with the logs, it was just hard for me to see how meaningful it all was. Encouraging them to do more just wasn't feasible for them*]. While physicians appreciated that the strategy was suitable for the majority of their patients, there was still mention of the challenge to effect sustainable behavior change in some of their patients (ST 4.6), and hesitation to involve these patients [*And not that I give up on my patients, but you have to think a patient whose 50 or 60... they've had 50 years of bad behavior probably. It's not that we don't continue to try, but it's a lot more difficult*].

Theme 5: Implementation and Sustainability Post Trial

Many participants reported sustained physical activity increases after the 1-year intervention [*It got me moving, and I am still even doing it today*]. More than half who increased step counts indicated continued pedometer use, while others discussed setting objectives for themselves without needing the pedometer (ST 5.1) [*I walk 20 minutes out and then 20 minutes back at least 3-4 times per week*]. By the end of the intervention, some appeared more intrinsically motivated [*Yes, since the research, and the end of the research, there is a definite motivation to go walk, and when I don't walk, for many different reasons, I feel guilty for not walking. So really the research was greatly motivating*]. Some made additional efforts to increase their step counts further after completing the trial [*Even more, and when it's not nice outside, I bought myself a treadmill, so that way I get enough*].

Several were encouraged by the realization that regular walking can lead to measurable health improvements (ST 5.2) [*I found that it was helpful because it demonstrated to me the need to walk more and the results that come from that additional exercise. I subsequently lost weight, and felt better, and it has been an inspiration for me long after the study concluded to continue to be aware of the need to walk more and eat less and to continue to lose weight*].

Post-study derailment was more common in participants unable to increase step counts. They cited lack of accountability to the study and their physician as a reason for not continuing (ST 5.3) [*I'm not being forced to give my results to anybody, so nobody really sees whether I walk or not, so it's easier for me not to walk*]. Termination of the study also impacted their motivation [*Like I mean, at first I was motivated to see the improvement myself, you know, and then after that I felt like I had no more commitment, you know, to the program and to (the trial coordinator), and then I kept sliding, and sliding, and sliding*].

For some physicians, the strategy became an additional task they felt they could not and did not manage in the absence of external support (ST 5.4) [*We are in busy clinics, and we have certain checklists in our mind of things that we have to do, so adding this extra makes it a little harder*]. Others physicians continued to discuss step counts with their patients, but without a formal prescription [*The 10,000 steps was a goal that both of them achieved, so it's just again, in the context, I'll say where are you at. We talk about their averages*].

Physicians were supportive of implementing the intervention on a larger scale (ST 5.5) but with a substitute for trial coordinator support [*If you could integrate it, either the nurse or a dietitian, they don't necessarily have to be a study coordinator, but I mean if you can integrate it into part of natural aspect of care which includes not only the physician*]. They acknowledged the value of having a physician deliver the intervention, but mentioned there could be a valuable role for nurses or other clinic staff (ST 5.6) [*I think having the physician's seal of approval does help, but having the details discussed with the nurse is often better because I think*

people are franker about their questions or their misgiving and all that, because they tend to put on a smiley face for us (laughs)].

4.2.5 Discussion

SMARTER demonstrated that a physician-delivered step count prescription strategy favourably impacts daily step counts, glycemic control and insulin resistance. The present qualitative study ascertained that those who increased step counts perceived the goal setting component, formalized as a step count prescription, to be a helpful means of increasing activity levels, in combination with pedometer-based monitoring. They adopted strategies to integrate more steps into their routines and, while poor weather constituted a challenge to outdoor steps, they were able to find alternatives to reach step goals. Many observed health improvements that they attributed to higher step counts, motivating them further. Those who did not increase their overall counts did acknowledge the merits of the approach and indicated attempts to increase walking levels; however, work constraints, health limitations, and poor weather were key barriers in this group. Physicians indicated that the approach provided a concrete means of discussing and monitoring physical activity, but they highlighted that in order to implement the strategy into usual practice, they would require support from other clinic staff similar to what the SMARTER trial coordinator provided.

Many of the facilitators and barriers identified are consistent with other qualitative evaluations of pedometer-based interventions[9-13]. The regular monitoring offered by pedometers and tailored goal setting is consistently valued by participants, which is in line with findings from meta-analyses of pedometer-based interventions demonstrating higher step counts when goals were provided[2,14]. Health limitations, work constraints, and weather are regularly cited, and also emerged as barriers in our study. Few studies

have explored the experiences of end-users involved in a pedometer-based intervention delivered in a primary care setting[10,13,15].

Harris and colleagues interviewed 30 older adults after a 12-week intervention consisting of four tailored physical activity consultations with a practice nurse, with monitoring of step counts (PACE-lift trial)[13]. Nurses were trained to apply behavior change techniques[16] however; the step count increases and reported barriers were similar to those in SMARTER. In the extension of this trial (PACE-UP), nurse-delivered support was compared to postal delivery of pedometers. While nurse support during the 12-week intervention led to a 2-fold higher increase in step counts, the two arms were comparable at a 1-year follow-up[9]. This suggests that ongoing support and accountability is important, which was also indicated in our study.

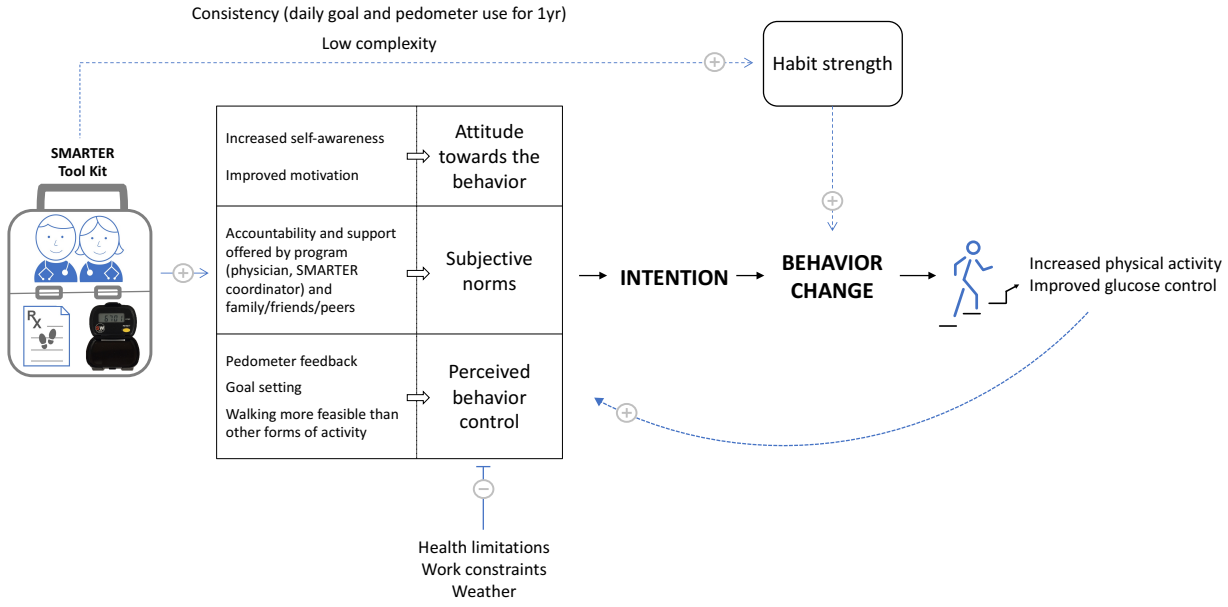
In the "Green Prescription" program in New Zealand, the role of the physician was to refer patients to counselors and provide a physical activity time-based prescription. Over the following 3-4 months, the counselor provided telephone-based or face-to-face support[17,18]. Again, this approach has achieved success in meeting physical activity guidelines in shorter term follow-up but was not sustained at 2-3 years [18]. Another trial demonstrated that 90-minute group sessions led by clinical psychologist with a background in behavior change can augment effects of pedometer-based self-monitoring. However, such sessions are not routinely integrated into clinical practice[19]. Greater involvement from the physician in a primary care, as in our SMARTER trial, offers the ideal setting to provide greater support and continuity of physical activity monitoring for patients. This is in line with the Diabetes Canada's recommendation for physician-delivered exercise prescriptions[20]. However, our qualitative study findings indicate that this may require more support within the clinic setting to reduce the burden for the physician. The Exercise is Medicine initiative, which promotes physician-delivered

exercise prescription in general[21], further encourages the involvement of allied health professionals as 'physical activity intervention advisors' who can receive training to provide more in-depth counseling and follow-up with patients.

Weather is frequently reported as a barrier to physical activity, especially in more northern climates[10,22], as in our study. However, many participants were able to overcome weather-related barriers by walking more indoors, either at home or in shopping malls, or using exercise equipment such as a treadmill or elliptical to accumulate the steps. This may have been facilitated by the tailored nature of the prescription, and the emphasis on meeting a certain target on a daily basis.

We considered participants' perspectives in the context of two relevant theoretical frameworks (Figure 1).

Figure 1. Theory-Based Schematic Illustration of SMARTER Participant Perspectives



The Theory of Planned Behavior has been applied in evaluations of health-related behavior change interventions, including those involving walking[23-25]. The theory focuses on the intention-behavior relationship, such that intent is shaped by *attitude*; *subjective norms*, referring to perceptions of others' expectations and willingness to meet these; and *perceived behavioral control*, or the belief that they have the skills, ability, willpower, time, and support to be more physically active[26]. Our participants generally expressed positive attitudes towards walking, and the health benefits associated with achieving higher step counts. Support from friends and family, as well as from the study coordinator was deemed important. For many participants, the strategy positively impacted perceived behavioural control; walking and step counting were generally viewed as feasible and facilitated by pedometer-based monitoring and goal-setting through the prescription. However, poor weather, work constraints and health limitations emerged as barriers that were not addressed by the strategy for some participants.

Moreover, consciously developing the intention may not be sufficient to change behavior, as unconscious processes may also be at play. Through the lens of the Dual Process Theory, we also considered habit, which has been recognized as important driver for sustainable behavior change involving physical activity[216,217]. Several participants spoke about developing new habits to integrate more steps into their daily activities and have maintained these habits after trial completion. This was likely facilitated by the consistency of the program (i.e., having a daily goal for 1 year), and the general ease of performing the task (low complexity)[27]. Wearing the pedometer daily became a habit for many participants. Interestingly, more than half of the participants who increased step counts continued to wear the pedometer after the intervention.

As we explored physicians' responses and willingness to adopt the strategy, we considered Roger's diffusion of innovation theory[29]. This theory has been widely applied

in clinical practice to understand the dynamics related to the diffusion and adoption of new practices, including health promotion strategies[30,31]. Physicians acknowledged the *relative advantage* of step count prescriptions compared to their usual physical activity recommendations: it offered a realistic framework for physical activity discussions, and patients were more responsive. The outcomes of the strategy were also *visible* to physicians, particularly the impact the strategy had on their patient's motivation to be physically active. The strategy was also perceived as being in line with their views on exercise promotion, and *compatible* with their practice and structure of care. However, the compatibility and *degree of perceived difficulty* may have been influenced by the support they received from the study coordinator. Some physicians expressed that reviewing the log books, and discussing the program with the patient would be difficult within the time constraints of the clinic visit without additional support from the coordinator. The reliance on external help may have impacted the *trialability* of the strategy, as physicians did not continue with the prescriptions after the trial end. Future work will be needed to either simplify the process for physicians so that can be included as part of their "usual checklist", and potentially involve members of the health care team who can help in a similar manner as the study coordinator. Capillary blood glucose monitoring among patients on insulin therapy is an example of an aspect of care that often involves various members of the health team. Typically, the nurse demonstrates glucometer use, and the patient maintains a record, and may be reminded to bring in the written or digital record by the clinic clerk. Analogously, the implementation of a step count prescription strategy into clinical practice may require a clinic nurse or other health professional to demonstrate use of the pedometer and provide additional encouragement and support in person or by telephone, and clinic administrative staff who could remind patients to bring their logs, and include a copy of the prescription form in the patient chart.

We acknowledge certain limitations of our approach. We conducted interviews only with participants who completed the intervention so that we could assess successful and less successful cases in terms of step count improvements; however, the views of participants who dropped out may be different. The interviews with participants were conducted by telephone instead of face-to-face with participants as telephone-based discussions were most convenient for them. We have not explored the views of physicians who chose not to participate; however, we purposely included some physicians who had recruited fewer patients. Lastly, the average length between trial completion and the interviews was just over a year. While this may have led to some recall bias among participants, this time frame allowed us to also assess the sustainability of the intervention and provided a better idea of the effect of the time elapsed on developed habits.

4.2.6 Conclusion

The experiences shared by SMARTER participants and physicians indicate that the framework for discussion, target setting, and accountability of the strategy could explain its ability to facilitate step count increases. The main barriers impeding improvements in step counts included health limitations, work constraints, and poor weather. The strategy could be easily integrated into the patient-physician encounter but with the involvement of other members of the health care team. This support may allow physicians to feel more supported and motivated to continue engaging in the strategy over time and may amplify the impact of the intervention. This topic is an important area of future research.

4.2.7 Acknowledgements

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4.2.8 Conflicts of Interest

None.

4.2.8 References

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4.3 Preamble – Manuscript 2

Our qualitative study focused on the acceptability of the strategy components, as well as the sustainability and feasibility for implementation of the strategy into clinical practice. We obtained valuable input from trial participants and collaborating physicians which will help to refine the strategy for future implementation and will inform other physical activity strategies in clinical practice. In conducting these interviews, it was clear that participants had responded differently to the strategy –in a way, they had followed different 'trajectories'. This motivated me to identify patterns of step counts during the intervention using daily step count data participant log books. To carry this out, I applied GBTM, a useful method for identifying groups of individuals that follow statistically similar trajectories over time. I was specifically interested in evaluating factors (demographic or clinical variables) that influence the response to the intervention by examining associations with membership to the different trajectories. This work was published by the *Journal of Science and Medicine in Sport* on April 18, 2020.

4.4 Content – Manuscript 2

A Trajectory Analysis of Daily Step Counts During a Physician-delivered Intervention

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4.4.1 Abstract

Objectives: Higher steps are associated with lower mortality and cardiovascular event rates. We previously demonstrated that tailored physician-delivered step count prescriptions successfully increased steps/day in adults with type 2 diabetes mellitus (T2DM) and/or hypertension. In the present analysis, we examined patterns of step count change and the factors that influence different responses.

Design: Longitudinal observational study

Methods: Active arm participants (n=118) recorded steps/day. They received a step count prescription from their physician every 3-4 months. We computed mean steps/day and changes from baseline for sequential 30-day periods. Group-based trajectory modeling was applied.

Results: Four distinct trajectories of mean steps/day emerged, distinguishable by differences in baseline steps/day: sedentary (19%), low active (40%), somewhat active (30%) and active (11%). All four demonstrated similar upward slopes. Three patterns emerged for the change in steps from baseline: gradual decrease (30%), gradual increase

with late decline (56%), and rapid increase with midpoint decline (14%); thus 70% had an increase from baseline. T2DM (odd ratios [OR]: 3.7, 95% CI 1.7, 7.7) and age (OR per 10-year increment: 2, 95% CI 1.3, 2.8) were both associated with starting at a lower baseline but participants from these groups were no less likely than others to increase steps/day. **Conclusions:** T2DM and older age were associated with lower baseline values but were not indicators of likelihood of step count increases. A physician-delivered step count prescription and monitoring strategy has strong potential to be effective in increasing steps irrespective of baseline counts and other clinical and demographic characteristics.

4.4.2 Introduction

Increments of as few as 1,000 steps/day are associated with lower mortality[1,2] and lower cardiovascular disease event rates[3]. On average, individuals with chronic diseases such as type 2 diabetes (T2DM) and hypertension do not achieve step count recommendations[4-6]. We conducted a randomized controlled trial, Step Monitoring to improve ARTERial Heath (SMARTER) that demonstrated a physician-delivered step count prescription strategy combined with pedometer-based monitoring increases daily steps in overweight patients with T2DM and/or hypertension, as well as improves glycemic control and insulin resistance. Step count changes were quantified in both active and control arms with 1 week of pedometer measurement before and after the 1-year intervention period. Compared to control arm participants (usual care), active arm participants increased daily step counts by 1200, a 20% increase over their baseline, an increment previously shown to be associated with mortality reduction[7].

In the spirit of precision medicine, understanding which subgroups were most responsive will enable us to better target the step count prescription approach and to

develop strategies to enhance effects in less responsive subgroups. In the present analysis, we used the step count log books of active arm participants to derive trajectories of both steps/day and changes from baseline steps/day over the 1-year intervention. We also examined indicators of trajectory membership. We hypothesized that individuals with T2DM, women, older individuals, and those with higher body mass index (BMI) would be more likely to belong to a lower activity trajectory, given prior evidence that these individuals have lower physical activity levels[8-10].

4.4.3 Methods

The SMARTER trial (clinicaltrials.gov NCT01475201) was approved by McGill University's Faculty of Medicine Institutional Review Board and individual informed consent was obtained.

Participants were overweight or obese ($25\ kg/m^2 \leq BMI < 40\ kg/m^2$) with T2DM and/or hypertension. None had gait abnormalities. Detailed inclusion and exclusion criteria for the trial have been reported previously[7,11]. The overall goal was a net increase of 3,000 steps/day above baseline over 1 year, with a slower rate of increase in more sedentary participants. Participants were provided with Yamax-200 pedometers (StepsCount, Ontario, Canada) for daily monitoring.

In the present analysis, we used self-reported step count data entered into log books from those randomized to the step prescription arm. Days that were missing a step count entry were entered as blank cells; all other step entries were considered valid (i.e., no minimum threshold was applied). The average steps/day for each consecutive 30-day period over 12 months (T1-T12) was calculated by dividing the sum of step counts by the number of valid days in the 30-day period. Periods with more than 50% of days without data were classified as missing.

We then applied group-based trajectory modeling (GBTM)[12], with models fit for 1-8 groups. First, we examined the mean steps/day for each sequential 30-day period over 1 year. Second, we computed the difference between each of the 30-day mean steps/day and the baseline steps/day value; we then applied GBTM analysis to this series of difference in mean steps/day from baseline values. For both of these analyses, we selected models with both a high Bayesian Information Criterion (BIC) and at least 10 members per group. BIC values were also used to determine the appropriate trajectory shape (constant, linear, quadratic). Model fit was verified by confirming a high average posterior probability of group membership for each of the groups (>0.7). GBTM analyses were conducted in SAS (version 9.4) using the TRAJ package developed by Jones and Nagin[13].

Next, cumulative logistic regression models were used to identify predictors of trajectory group membership. This was performed separately for each of the trajectory analyses. We were particularly interested in evaluating T2DM as a predictor given the lower levels of physical activity in this population[4,5]. We considered other variables that in prior studies have been reported to influence physical activity levels and step counts in the general population[8,9] and adults with T2DM[10]. These included baseline age, sex, ethnicity (European origin or other), university education (yes/no), BMI, cardiorespiratory fitness (VO_2 peak), and the season during which the intervention was started. Season was defined using the meteorological calendar: fall (September-November), winter (December-February), spring (March-May), and summer (June-August). Seasons were then collapsed as Fall-Winter and Spring-Summer.

For each of the two analyses, variables with possible associations with lower step count trajectory in univariable analyses ($p<0.15$) were considered for inclusion in a multivariable cumulative logistic regression model. We confirmed graphically that the

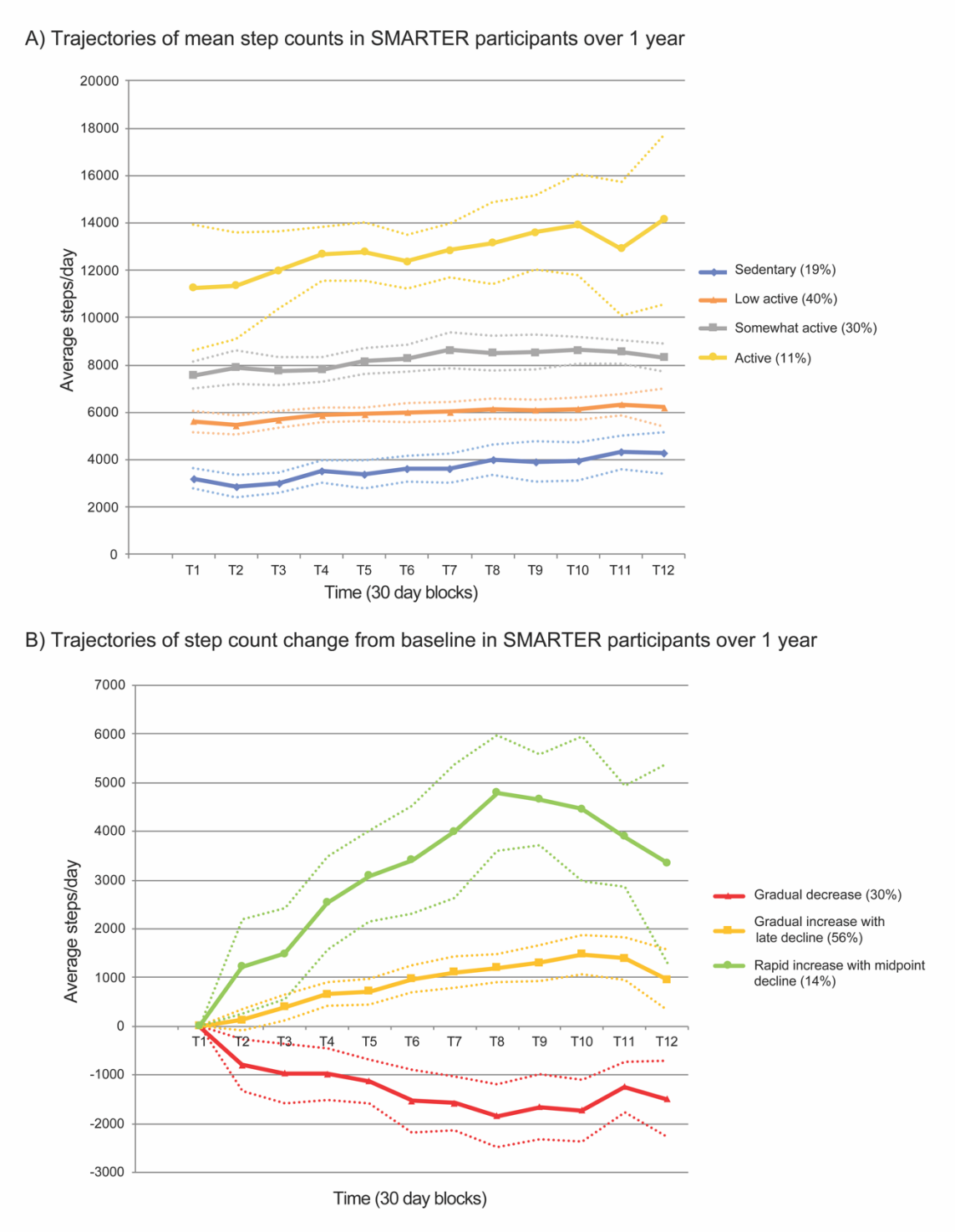
proportional odds assumption was applicable, with an empirical logit plot to assess whether the cumulative logits for each predictor variable were parallel. As distinct from conventional logistic regression, in cumulative logistic regression the odds ratio (OR) generated is a summary of the ORs obtained from separate binary logistic regressions using all possible cut points of the ordinal outcome (group 1 vs 2, 3, 4; 1, 2 vs. 3, 4; 1, 2, 3 vs. 4)[14]. Probabilities are cumulated over lower ordered values; therefore, the ORs are interpreted as the probability of being in a lower step count trajectory.

4.4.4 Results

In the SMARTER trial, 174 participants were randomized to the active arm, among whom 135 completed final evaluations (77.5%). Of those who completed their final trial evaluations, step count log books were submitted by 108 participants (80%). We also incorporated data from the log books of 10 participants out of the 39 participants who did not complete their final trial evaluation (25.6%). Because SMARTER was a pragmatic trial, we did not alter the scheduling of the physician visits for our trial. As a result, the time varied between the baseline evaluation/randomization and the initial physician visit where participants received the pedometer and step count prescription. Final trial evaluations were scheduled to occur after 1-year, and delayed timing of the first physician visit led to 49 participants not having a full year of step count tracking (Supplementary Table 1). There were no important differences between active arm participants included in the analysis and those excluded from the analysis, due to not returning their log books (Supplementary Table 2). Among participants who submitted their log book, over 80% maintained these for the duration of the intervention (Supplementary Figure 1).

The model with the best fit for trajectories of absolute steps/day included 4 trajectory groups with an average posterior probability of group assignment greater than >0.94 in each of the groups, indicating very good fit (Figure 1). The initial points of each trajectory (T1) closely matched the widely-used classification scheme for categorizing step counts into activity levels (sedentary <5000, low active 5000-7499, somewhat active 7500-9999, active >10,000)[15]. Therefore we labelled the derived trajectories according to this scheme.

Figure 1: Trajectories of (A) mean step counts and (B) step count change from baseline in SMARTER participants over 1 year



Percentage reflects the proportion of participants in each step count trajectory group, based on the sum of all posterior probabilities for that group. Dotted lines represent the 95% confidence interval.

The slopes of all trajectories were positive, reflecting an average increase in daily steps over 1 year in each of the 4 groups. The trajectory slope for the most active group was the greatest in magnitude (236, 95% CI 150, 323) and conclusively higher than the sedentary (mean difference 117, 95% CI 2, 232), low active (mean difference 157, 95% CI 53, 262), and somewhat active group (mean difference 143, 95% CI 38, 248). The trajectory slope of the least active group (sedentary group: 119, 95% CI 51.2, 187.2) was higher than the low active (79, 95% CI 31, 129) and somewhat active groups (93, 95% CI 39, 146), but not conclusively different (mean difference sedentary vs. low active: 40, 95% CI -47, 127 and sedentary vs. somewhat active: 26, 95% CI -62, 114).

The characteristics of participants in each trajectory group are shown in Table 1.

Table 1. Participant characteristics by trajectories of mean step counts

	Overall	GBTM trajectories of step counts over 1-year			
	(n=118)	Trajectory 1 *Sedentary* (n=23)	Trajectory 2 *Low Active* (n=46)	Trajectory 3 *Somewhat Active* (n=36)	Trajectory 4 *Active* (n=13)
Age, years, mean (SD)	60.9 (11.3)	66.4 (11.8)	62.6 (10.5)	57.2 (10.9)	55.7 (10.9)
Women, N (%)	65 (55%)	13 (57%)	25 (54%)	22 (61%)	5 (38%)
University education, N (%)	53 (45%)	10 (44%)	24 (52%)	15 (42%)	4 (31%)
European origin, N (%)	78 (67%)	14 (61%)	32 (71%)	24 (67%)	8 (62%)
Body mass index, kg/m², mean (SD)	31.7 (4.7)	32.3 (4.2)	32.0 (4.3)	31.5 (5.8)	30.0 (3.1)
Type 2 diabetes mellitus, N (%)	68 (58%)	19 (83%)	29 (63%)	14 (42%)	5 (38%)
Hypertension, N (%)	113 (96%)	22 (95%)	45 (98%)	34 (95%)	12 (92%)
Baseline daily pedometer steps, steps/day, mean (SD)	4606 (2160)	2520 (1162)	4140 (1517)	5804 (1916)	6623 (2405)
Peak Oxygen Consumption (ml/kg/min), mean (SD)*	23.2 (6.8)	20.6 (7.0)	21.6 (5.9)	25.3 (5.4)	29.3 (7.9)
Spring-Summer Start, N (%)	44 (37%)	8 (35%)	18 (39%)	13 (36%)	5 (38%)

*Only measured in a subgroup of patients n=68 (n=16, n=27, n=17, n=8 for trajectory groups 1, 2, 3, and 4, respectively)
GBTM, group-based trajectory modeling; N, number; SD, standard deviation

In the evaluation of indicators of steps/day trajectory membership, T2DM status and age were predictors of group membership in a model that also included sex and BMI; participants with T2DM were 3.7 times (95% CI 1.7, 7.7) more likely to be in a less active step count trajectory compared to those without T2DM (Supplementary Table 3). Similarly, older participants were more likely to be in a lower step count trajectory: for a 10-year increase in age, the odds of being in a more sedentary trajectory was twice that of being in a more active trajectory (95% 1.3, 2.8). In the smaller subgroup of participants with VO_2 peak data, we observed higher values to be associated with membership to a more active trajectory. Specifically, in a model adjusting for age, a 1-unit (mL/min/kg) increase in VO_2 peak was associated with 10% lower odds of being in a lower step count trajectory (OR 0.90, 95% CI 0.83, 0.98)(Supplementary Table 3).

In the analysis of trajectories of step count change from baseline, the model yielding the best fit consisted of 3 distinct trajectory groups. Based on shape, we labelled these as (1) gradual decrease (2) gradual increase with late decline and (3) rapid increase with midpoint decline (Figure 2). The average posterior probability of group assignment was greater than >0.96 in each of the 3 groups. One third of participants (30%) experienced a gradual decrease in steps over 1 year, and two-thirds experienced an increase: in 56% overall, the increase was gradual with a late decline, and in 14% the increase was steep and more rapid, peaking at approximately 8 months and declining afterwards, but remaining well above baseline levels. Characteristics of participants in each trajectory group are presented in Table 2.

Table 2. Participant characteristics by trajectories of step counts change from baseline

	GBTM trajectories of step count change from baseline		
	Trajectory 1 *Gradual Decrease* **(n=34)**	**Trajectory 2** *Gradual Increase with Late Decline* **(n=64)**	**Trajectory 3** *Rapid Increase with Midpoint Decline* **(n=16)**
Age, years, mean (SD)	59.0 (10.6)	62.8 (10.8)	57.6 (13.6)
Women, N (%)	19 (56%)	35 (55%)	8 (50%)
University education, N (%)	18 (53%)	29 (45%)	3 (19%)
European origin, N (%)	12 (37%)	23 (36%)	2 (25%)
Body mass index, kg/m², mean (SD)	31.4 (5.5)	31.8 (4.2)	30.9 (3.2)
Type 2 diabetes mellitus, N (%)	19 (56%)	37 (58%)	10 (63%)
Hypertension, N (%)	33 (97%)	61 (95%)	15 (94%)
Baseline steps, steps/day, mean (SD)	4778 (2149)	4447 (2013)	4292 (2536)
Peak Oxygen Consumption (ml/kg/min), mean (SD)*	21.5 (6.3)	23.1 (5.9)	29.9 (10.2)
Spring-Summer start, N (%)	23 (68%)	20 (31%)	1 (6%)

*Only measured in a subgroup of patients (n=24, n=36, n=7 for trajectory groups 1, 2, and 3, respectively)
GBTM, group-based trajectory modeling; N, number; SD, standard deviation

T2DM was not associated with trajectory membership, nor were sociodemographic characteristics, baseline step counts, BMI, or hypertension (Supplementary Table 4). Seasonal period was associated with trajectory membership: those in the decreasing trajectory were 6.5 times (95% CI 2.8, 14.9) more likely to have started the intervention in the spring and summer, compared to those in the increasing trajectories. This association persisted after adjusting for age, sex, BMI, university status and T2DM status. Participants in a decreasing trajectory were also twice as likely to have a university education compared to participants in the increasing trajectories [OR 2.1 (95% CI 1.01, 4.40)], which persisted after adjusting for season start. In univariable analyses, a 1-unit (ml/min/kg) increase in VO_2 peak was associated with 8% lower odds of being in a decreasing trajectory (OR 0.92, 95% CI 0.85, 0.99), but this association did not persist when adjusting for season start [OR 0.96 (95% CI 0.88, 1.03)].

4.4.5 Discussion

Our analyses delineated four trajectories of absolute steps/day over the course of a 1-year physician-delivered step count prescription strategy. The trajectories were stratified as a function of initial step count levels. The slope of the increase was comparable across groups indicating that the overall increase in steps/day observed was not restricted to either the more active or less active groups. We further identified three trajectories of step count changes relative to baseline. In contrast to the absolute step count trajectories, these differed in shape and course, with one demonstrating a rapid increase with midpoint decline, another a gradual increase with a late decline, and the third a gradual decrease. Interestingly, the trajectory demonstrating a rapid increase in steps showed nearly a 5,000 step increase by the 8 month time point, which exceeded the intervention target of 3,000 steps/day. This higher step count level was not sustained, but there was still an overall

increase of 3,000 steps/day from baseline. Participants with T2DM were more likely to be in a lower level trajectory of absolute step count trajectories but the presence of T2DM was not associated with pattern of change from baseline steps. Associations of older age with trajectories paralleled those of T2DM. These findings indicate that although individuals with T2DM and older individuals may start at a lower absolute value for steps/day, they are no less likely than others to respond to a physician-delivered step count prescription strategy.

The importance of a steps/day increase is highlighted by recent studies that demonstrate mortality benefits associated with even small increases in steps. Among 16,741 older women who wore an accelerometer for 7 days as part of the Women's Health Study, walking as few as 4,400 steps/day was associated with a 41% reduction in all-cause mortality, compared to women walking fewer than 1,700 steps/day[2]. Importantly, 1,000-steps/day increments were associated a 15% reduction in mortality[2]. Furthermore, results from a large study in free-living middle-aged and older men and women demonstrated that any increase in steps over an average follow-up period of 3.7 years was associated with a 61% lower all-cause mortality compared to a decrease in steps, independently of age, sex, baseline step counts and BMI change[1]. Our findings in the present analysis are consistent with the overall increase in steps/day that we observed for the active intervention vs. control arm in the original SMARTER trial[7], and further demonstrate that step count improvements are achieved across levels of baseline activity.

We applied GBTM, a method that allowed us to identify different trajectories of steps and explore predictors associated with trajectory membership in a single model. The majority of other studies examining patterns of step counts during a physical activity intervention have grouped everyone into a single group or compared trajectories among predefined groups based on by age, sex or other relevant characteristics[16-18]. Similarly to

our study, Imes and colleagues used GBTM to evaluate trajectories during a 1-year weight loss intervention[19]. Interestingly, they identified 4 trajectories of mean step count change over the 1-year that resembled our 4 trajectories in terms of baseline activity level. However, in contrast to our findings, they noted that only individuals belonging to the active trajectory (>10,000 steps/day at baseline) were able to increase daily steps over the course of the intervention, while the other groups either maintained or decreased daily steps. Pedometer use was recommended, but not required. In contrast, in SMARTER, pedometer use was the key intervention component. All aimed to achieve the same net increase over 1 year, but rate of step count increase was tailored to the participant's baseline activity level, with a slower rate in more sedentary participants. This individualized approach may have facilitated a greater increase in sedentary participants, who might not have made efforts to increase their steps otherwise. Overall, exploring patterns of change during a step count intervention captures important information about the variability of the response and provides a more complete understanding of its effectiveness. With the increasing number of physical activity trials and step count monitoring, GBTM is a valuable but underused method for exploring physical activity patterns.

In our study, participants who started the intervention in the fall and winter were more likely to be in an increasing trajectory, compared to those who started in the spring and summer. In general, fall and winter in Canada is associated with lower activity levels than spring and summer. For example, in a previous longitudinal analysis of 166 individuals with T2DM, we observed a 15% reduction in steps during the fall/winter months compared to spring/summer[20]. In the SMARTER trial, baseline steps/day were higher for participants who started in spring/summer (mean 6795 steps/day, 95% CI 6245-7245) than those who started in fall/winter (5850 steps/day, 95% CI 5493-6206) in

fall/winter (between season difference -945 steps: 95% CI -1521,-370)[21]. Thus, for those starting in fall/winter, moving towards spring/summer may have augmented the steps/day increase stimulated by the intervention itself; this may result in a more pronounced change from baseline. In our qualitative follow-up of the SMARTER trial[22], poor weather was reported as a barrier to physical activity, particularly among participants who were unsuccessful in increasing their step counts. When possible, in colder climates, there may be some advantage to starting the intervention in the fall/winter, addressing weather barriers early (e.g., indoor walking, warm outdoor wear) and launching patients on an upwards trajectory.

Additional support mechanisms may help to amplify the effects of the intervention and ensure a sustained increase in steps. Our group is working towards an enhanced strategy that will involve between-visit virtual coaching by a health professional, peers or both. New Zealand has successfully incorporated similar elements into their Green Prescription initiative, a government-funded physical activity prescription program delivered by health care professionals and integrated into clinical practice[23]. Our qualitative follow-up of the SMARTER trial indicated that support and accountability from the physician influenced participant motivation[22]; however, creating additional partnerships between patients may provide an added level of accountability that could further enhance engagement. In this context, a web or app-based step count tracking platform that enables the creation of peer groups could also be integrated for additional motivation and support. Physical activity monitors now enable the wireless and 'real time' monitoring of activity levels and intensity, and sedentary behavior. The ease of monitoring for participants and more efficient data collection methods for researchers will greatly support future research evaluating physical activity patterns, and

importantly, will enhance engagement and promote adherence to the intervention over time.

The following limitations of our study should be considered. When SMARTER was started in early 2012, affordable pedometers did not have Bluetooth or wireless capabilities. While we performed a blinded assessment of step counts pre- and post-intervention (pedometer with viewing window concealed for measurement), we relied on self-reported pedometer data for the present analysis. This may result in over-reporting of steps among some participants. Furthermore, participants who did not return their step count log book could not be included in this analysis. However, there were no important differences between active arm participants who were included or excluded from the analyses. Many of the participants dropped out from the intervention for reasons unrelated to physical activity, but it is also possible that these participants would have impacted the trajectories we observed. We were not powered to evaluate the impact of different trajectories on health outcomes, although we did observe an overall improvement in glycemic control and insulin resistance alongside step counts in active compared to control arm participants in the original trial[7].

In conclusion, a physician-delivered step count prescription and monitoring strategy has strong potential to be effective in increasing steps irrespective of baseline counts and other clinical and demographic characteristics. Larger studies will also be needed to evaluate the impact of different patterns of step count change on health outcomes. This topic is an important area for future research in view of the associations of even small step count increments with cardiovascular disease reductions and longevity[1,3].

4.4.6 Acknowledgements

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4.4.7 Conflicts of Interest

The authors have no conflicts of interest.

4.4.8 References

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4.5 Supplemental Material – Manuscript 2

Supplementary Table 1. Number Participants Contributing Data for Group-Based Trajectory Modeling Analysis at Each Time Point

	Time (30-day blocks)											
	T1	**T2**	**T3**	**T4**	**T5**	**T6**	**T7**	**T8**	**T9**	**T10**	**T11**	**T12**
Number of participants with >50% data at each time point	114	114	114	114	106	103	101	98	92	80	71	49
Participants with <50% data at each time point	4	4	4	3	10	11	12	12	14	20	16	11
Number of drop outs	0	0	0	1	2	4	5	6	7	7	8	9
Number of participants who completed Study <1 year	0	0	0	0	0	0	0	2	5	11	23	49
Percentage of enrolled participants with >50% data	97 %	97 %	97 %	97 %	91 %	90 %	89 %	87 %	87 %	80 %	82 %	82 %
Number of participants with >50% data by trajectory group												
Group 1	23	22	21	21	21	18	17	16	16	14	14	12
Group 2	45	44	46	44	42	40	42	41	39	32	26	16
Group 3	34	35	34	36	32	31	31	29	27	25	23	17
Group 4	12	13	13	13	12	13	12	12	10	9	8	4

Supplementary Table 2. Characteristics of Participants Included/Excluded in the Step Count Trajectory Analysis, and the Complete SMARTER Active Arm Cohort

	Full Cohort of Active Arm Participants (N=174)	Active Arm Participants in Step Trajectory Analysis (N=118)	Active Arm Participants Excluded from Step Trajectory Analysis (N=56)	Comparison of Active Arm Participants Included vs. Excluded from Step Trajectory Analysis Mean difference (95% CI)
Age, years, mean (SD)	60.0 (11.2)	60.9 (11.3)	58.3 (11.1)	-2.6 (-6.2, 1.0)
Women, N (%)	99 (57)	65 (55)	34 (61)	6 (-10, 21)
University education, no (%)	79 (45)	53 (45)	26 (46)	1 (-14, 17)
European origin, N (%)	110 (64)	78 (67)	32 (57)	-9 (-24, 7)
Body mass index, kg/m², mean (SD)	31.7 (4.5)	31.7 (4.7)	32.0 (4.6)	0.3 (-1.2, 1.8)
Type 2 diabetes mellitus, N (%)	116 (67)	68 (58)	34 (61)	3 (-13, 19)
Hypertension, N (%)	161 (93)	113 (96)	48 (86)	-10 (-21, 1)
Baseline daily pedometer steps, steps/day, median [IRQ]	4550 (2230)	4606 (2160)	4443 (2378)	-163 (-877, 552)
Peak Oxygen Consumption (ml/kg/min), mean (SD)	23.2 (6.9)	23.2 (6.8)	23.1 (7.1)	-0.1 (-2.7, 2.6)
Season start (spring/summer), N (%)	77 (44.3)	42 (36)	26 (46)	10 (-5, 26)

N, number; SD, standard deviation.

Supplementary Table 3. Odds Ratios for Variables Predicting Membership in a Step Count Trajectory Group with Lower Baseline Activity Levels

Predictor Variables	Univariable Analysis Odds Ratio (95% CI) P-value	Multivariable Analysis A Odds Ratio (95% CI)	Multivariable Analysis B Odds Ratio (95% CI)	Multivariable Analysis C Odds Ratio (95% CI)
All participants (n=118)				
Presence of T2DM	3.37 (1.67, 6.80) P<0.001	3.23 (1.59, 6.56)	3.68 (1.75, 7.74)	
Presence of hypertension	1.86 (0.36, 9.52) P=0.458			
Age (years)	1.79 (1.34, 2.37) P<0.001	1.79 (1.34, 2.37)	1.97 (1.34, 2.59)	1.04 (0.99, 1.09)
Sex (women)	1.13 (0.58, 2.19) P=0.713		1.76 (0.85, 3.64)	
Body Mass Index (kg/m²)	1.05 (0.98, 1.13) P=0.197		1.06 (0.98, 1.14)	
University Level Education	0.74 (0.38, 1.44) P=0.373			
Ethnicity (European origin)	1.00 (0.50, 2.01) P=0.990			
Season start (spring/summer)	0.98 (0.49, 1.92) P=0.941			
Participants with cardiorespiratory data (n=68)				
Peak VO_2 (ml/kg/min)	0.88 (0.82, 0.94) P<0.001			0.90 (0.83, 0.98)

Comparison groups were: Presence of type 2 diabetes mellitus (absence of type 2 diabetes mellitus), presence of hypertension (absence of hypertension), sex (men), education (less than a university level education), ethnicity (non-European origin), season (Fall/Winter).

Multivariable analysis A includes variables with p-value <0.15 in univariate analyses
Multivariable analysis B includes variables with p-value <0.15 in univariate analyses as well as relevant covariates including BMI and T2DM
Multivariate analysis C only includes VO_2 peak and age (due to smaller sample size for peak VO2)

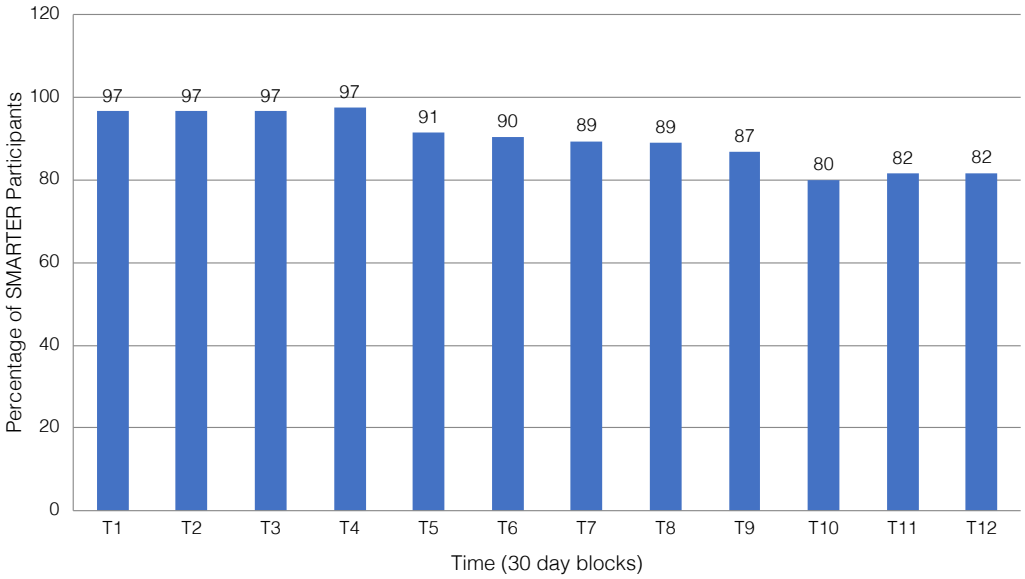
Supplementary Table 4. Odds Ratios for Variables Predicting Step Count Change Trajectory Group Membership

Predictor Variables	Univariable Analysis Odds Ratio (95% CI) P-value	Multivariable Analysis A Odds Ratio (95% CI)	Multivariable Analysis B Odds Ratio (95% CI)	Multivariable Analysis C Odds Ratio (95% CI)
All participants (n=114)				
Presence of T2DM	0.95 (0.46, 1.95) P=0.882		1.29 (0.58, 2.88)	
Presence of hypertension	1.65 (0.29, 9.57) P=0.576			
Age (years)	1.00 (0.96, 1.03) P=0.769		0.98 (0.95, 1.01)	
Sex (women)	1.13 (0.55, 2.32) P=0.774		1.99 (0.86, 4.62)	
Body Mass Index (kg/m²)	1.00 (0.93, 1.09) P=0.929		0.99 (0.91, 1.08)	
University Level Education	2.11 (1.01, 4.40) P=0.047	2.62 (1.20, 5.75)	3.49 (1.50, 8.14)	
Ethnicity (European origin)	0.79 (0.37, 1.68) P=0.542			
Season start (spring/summer)	6.48 (2.82, 14.93) P<0.001	7.36 (3.12, 17.39)	8.54 (3.54, 20.63)	6.89 (2.96, 16.03)
Participants with cardiorespiratory data (n=68)				
Peak VO_2 (ml/kg/min)	0.92 (0.85, 0.99) P=0.020			0.96 (0.88, 1.03)

Comparison groups were: Presence of type 2 diabetes mellitus (absence of type 2 diabetes mellitus), presence of hypertension (absence of hypertension), sex (men), education (less than a university level education), ethnicity (non-European origin), season (Fall/Winter).

Multivariable analysis A includes variables with p<0.15 in univariate analyses
Multivariable analysis B includes variables with p<0.15 in univariate analyses as well as relevant covariates including age, sex, BMI and T2DM
Multivariate analysis C only includes VO_2 peak and season start (due to smaller sample size for peak VO_2)

Supplementary Figure 1. Percentage of participants with >50% data per 30-day block



Expanded Methods

Procedure for calculating 30 day averages of steps/day:

(1) In SAS, separate datasheets were created for each participant which contained step count entries from log books (oriented vertically). Missing days were left blank.

(2) The total number of observations over the intervention was divided by 30 for each participant to determine how many observations were included in the final 30 day block (i.e., 12.1 meant that there 3 days in the last 30 day block). If there were less than 15 days (example <12.5) in this final 30 day block, the participant was flagged.

(3) 30 day averages were calculated for all participants as the sum of steps divided by the number of step count entries in the 30-day period. The last 30 day average was deleted in participants who had been flagged as having less than 15 days to ensure the final time period contained at least 50% data.

(4) Compliance was calculated for each 30 day average as number of cells with a step entry/number of cells in the period (30).

(5) A horizontal spreadsheet was created with the step count average at each time point for all participants (T1, T2, T3, etc.).

(6) For our main analyses, 30 day blocks with less than 15 days of step count entries were deleted (50%).

CHAPTER 5:

Impact of Intradialytic Pedaling Exercise on Arterial Stiffness

5.1 Preamble – Manuscript 3

In **Chapter 4**, we evaluated a physical activity promotion strategy that aimed to increase walking levels in sedentary to low active individuals with T2DM and/or hypertension. In response to the intervention, conclusive improvements in walking levels, glycemic control and insulin resistance were observed[15]. Interestingly, a reduction in arterial stiffness was observed but this was not conclusive, perhaps due to modest increase in step counts (1,200 steps/day). Regular physical activity is equally important in patients with CKD receiving hemodialysis, but adherence to regular exercise is especially poor in this population[111,112]. Pedaling exercise during dialysis (intradialytic pedaling) has been proposed as a realistic means to help patients achieve the cardiovascular health benefits of increased physical activity; it reduces sedentary time during dialysis and enables the accumulation of moderate physical activity in a supervised setting 3 times per week. Improvements in physical function, quality of life, and dialysis efficiency have been observed, however the results from studies examining the vascular benefits of intradialytic pedaling exercise are conflicting[116,122,227]. In the PEDAL trial, we evaluated the arterial health impact of intradialytic pedaling exercise in patients on a stable in-center hemodialysis regimen (*Manuscript 3*). This manuscript was published in March 2018 by the *American Journal of Hypertension*.

5.2 Content – Manuscript 3

The Impact of Intradialytic Pedaling Exercise on Arterial Stiffness: A Pilot Randomized Controlled Trial in a Hemodialysis Population

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5.2.1 Abstract

Objectives: Regular exercise is known to reduce arterial stiffness (AS) in hemodialysis patients. However, the impact of a more realistic intradialytic form of exercise, such as pedaling, is unclear. We aimed to examine 1) the effect of intradialytic pedaling exercise on AS over 4 months, and 2) the longer-term effect of pedaling on AS 4 months after exercise cessation.

Methods: Patients on stable in-center hemodialysis (3x/week) were randomly assigned 1:1 to either intradialytic pedaling exercise (EX) or to a control group receiving usual hemodialysis (nonEX) for 4 months. At baseline and 4 months, peripheral and central blood pressure (BP) indices, heart rate (HR), augmentation index HR corrected (AIx75), and carotid-femoral pulse wave velocity (cfPWV) were assessed (applanation tonometry). Measurements were repeated in the EX group 4 months post-exercise cessation.

Results: A per protocol analysis was completed in 10 EX group participants (58±17 years, body mass index [BMI] 26±4kg/m^2) and 10 nonEX group participants (53±15 years, BMI 27±6kg/m^2). Peripheral and central BP was unchanged in both groups. AIx75 was unchanged in the EX group, however a significant median increase of 3.5% [IQR 1.0, 8.5] was noted in the nonEX group (*P=0.009*). We noted a significantly greater absolute decrease in cfPWV in the EX group compared to controls: -1.00 [IQR -1.95, 0.05] vs. 0.20 [IQR -0.10, 0.90] (*P=0.033*). Interestingly, the decrease in cfPWV observed in the EX group was partially reversed 4 months after exercise cessation.

Conclusion: Intradialytic pedaling exercise has a beneficial impact on AS. This relationship warrants further investigation.

Clinical trials registration: clinicaltrials.gov #NCT03027778

5.2.2 Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in chronic kidney disease (CKD) patients on hemodialysis[1,2]. Accelerated arterial stiffness is an independent risk factor for CVD, especially in the CKD population, whose arteriosclerosis profile is accelerated compared to healthy aging[3]. Therefore, arterial stiffness can serve as a useful measure to evaluate the progression of vascular damage and CVD risk in a hemodialysis population.

Carotid-femoral pulse wave velocity (cfPWV) is recognized as the "gold standard" measure of arterial stiffness[4]. The association between cfPWV and vascular calcification is well-established[5], and studies have also indicated a step-wise relationship between cfPWV and the stages of CKD[6,7]. Furthermore, augmentation index (AIx), a measure of

wave reflection obtained through pulse wave analysis, is another independent predictor of declining renal function in patients with CKD[8,9].

A well-designed aerobic exercise program can favorably affect CVD risk factors, and regular aerobic exercise improves arterial stiffness in the general population and patients with CKD[10]. However, the arterial health impact of a more realistic intradialytic form of exercise, such as pedaling, remains unclear[5,11,12].

Therefore, we aimed to examine the effect of intradialytic pedaling exercise on cfPWV (primary outcome) and other arterial hemodynamic parameters over 4 months. We also aimed to evaluate the longer-term effect of pedaling on cfPWV and other arterial hemodynamic parameters 4 months after finishing the exercise intervention, as well as the impact on anthropometric measures, physical function, and routine laboratory blood markers.

5.2.3 Materials and Methods

Ethical Approval

The study was approved by the McGill University Health Centre (MUHC) ethics board; written informed consent was provided, and our study conformed to the standards of the Declaration of Helsinki[13].

Participants

We recruited adults with stage 5 CKD, who were on a stable in-center hemodialysis regimen (approximately 4 hours 3 times/week) for ≥12 weeks prior to recruitment. A recent cardiac evaluation (<1 year) was required to ensure adequate cardiac function to undergo the exercise program.

Exclusion criteria: 1) any physical or psychological disability that would impact study participation, 2) serum intact parathyroid hormone >250 pmol/L within 30 days prior, 3)

dysrhythmia or severe cardiac disease or peripheral arterial disease, 4) severe hyperkalemia (>6.5 mmol/L) for the last 2 weeks, 5) active cancer, 6) post-dialytic systolic blood pressure (BP) ≥160mmHg or diastolic BP ≥100mmHg within 4 weeks prior, or 7) anticipated living donor kidney transplant or other planned major surgery over the study duration.

Trial Design

We conducted a pilot multi-site, open-label, randomized-controlled clinical trial. Participants were assigned to either intradialytic pedaling exercise (EX) or to a control group receiving usual dialysis (nonEX) for 4 months, using stratified randomization based on age and sex (1:1 allocation ratio). Arterial stiffness, hemodynamic parameters, and other health measures were assessed in both groups within 2 days before and after the intervention.

The EX group was also re-assessed 4 months after completing the pedaling intervention to evaluate the sustainability of the pedaling effect. At the end of the 4 months, nonEX participants were given the opportunity to complete 4 months of pedaling following the same protocol as the EX group. They are included in a single-arm subgroup analysis to further examine the impact of pedaling exercise on arterial stiffness in a larger group of participants who followed the same exercise intervention.

Trial Procedures

Participants engaged in pedaling exercise 3 times/week during dialysis for 4 months. BP and heart rate (HR) were monitored during exercise (data not shown), and exercise time was recorded after each session. Due to the wide range of exercise capacity, participants in the EX group exercised for the amount of time that allowed them to reach the target range of 12-16 out of 20 points ("somewhat hard" to "hard") on the Borg Rating

of Perceived Exertion (RPE) Scale[14]. For safety, no patient exercised past the halfway mark of their dialysis session. Exercise compliance for each participant was calculated by dividing the number of dialysis sessions where pedaling was performed by the total number of sessions (48 sessions).

Arterial stiffness and hemodynamic parameters were measured in duplicate using applanation tonometry (SphygmoCor XCEL, AtCor Medical, Sydney, Australia), in a semi-supine position (20% inclination)[15,16]. Using an automated BP cuff, peripheral BP was measured; then by applying a validated generalized transfer function, the central pressure waveform is generated, allowing for measures of central BP, and AIx corrected for a HR of 75 beats/min (AIx75). Measurements of cfPWV were performed using the thigh cuff and carotid tonometry. Participants refrained from caffeine, alcohol and smoking at least 5 hours prior. Assessments pre- and post-intervention were all conducted prior to starting the mid-week dialysis session.

Gait speed was measured as the participant walked a 6-meter course as quickly as possible. The average of two timed readings was reported. Grip strength was measured using a hand dynamometer (Lafayette Instrument, Lafayette, IN, USA). Two readings were recorded in each hand, and the highest measure was reported.

Laboratory blood parameters including hemoglobin, leukocytes, platelets, serum albumin, serum electrolytes, total calcium, phosphate, parathyroid hormone levels, total cholesterol, triglycerides, high-density lipoprotein-cholesterol (HDL) (low-density lipoprotein-cholesterol [LDL] was calculated using the Friedewald formula), iron studies, and ferritin and were assessed at the same time as the baseline and final assessments. Single pool Kt/V was measured to quantify hemodialysis treatment adequacy. All blood analyses were performed at the MUHC Central Laboratories using standard methods.

Analytic Methods

Descriptive statistics were used to summarize participant characteristics using mean and standard deviation (SD), median and interquartile range (IQR), or percentages, as appropriate. Normality was assessed, and parametric or non-parametric tests were used accordingly. Per protocol analyses were performed on participants who completed the study. For our primary analyses, between-group comparisons (EX and nonEX groups) of the absolute difference [post- minus pre-intervention levels] were performed using a one-sided Mann–Whitney test to assess the superiority of pedaling exercise over usual hemodialysis. In secondary analyses, analysis of covariance (ANCOVA) was used to evaluate between-group comparisons of cfPWV (log-transformed) in a series of models adjusting for different covariates separately to avoid overadjustment, including age, Charlson comorbidity score, and the baseline cfPWV value. Between-group comparisons of baseline values were performed using two-sided Mann-Whitney test, and within-group comparisons of pre- and post-intervention values with a two-sided paired Student's t-test. The level of significance was set at $P<0.05$ and 95% confidence intervals (CI) were included when parametric tests were performed. SAS version 9.3 was used (SAS Institute, Cary, NC, USA).

5.2.4 Results

A total of 32 participants were initially randomized. Per protocol analyses were performed in those who completed the intervention (10 in each group)(Table 1).

Table 1 – Participant Baseline Characteristics

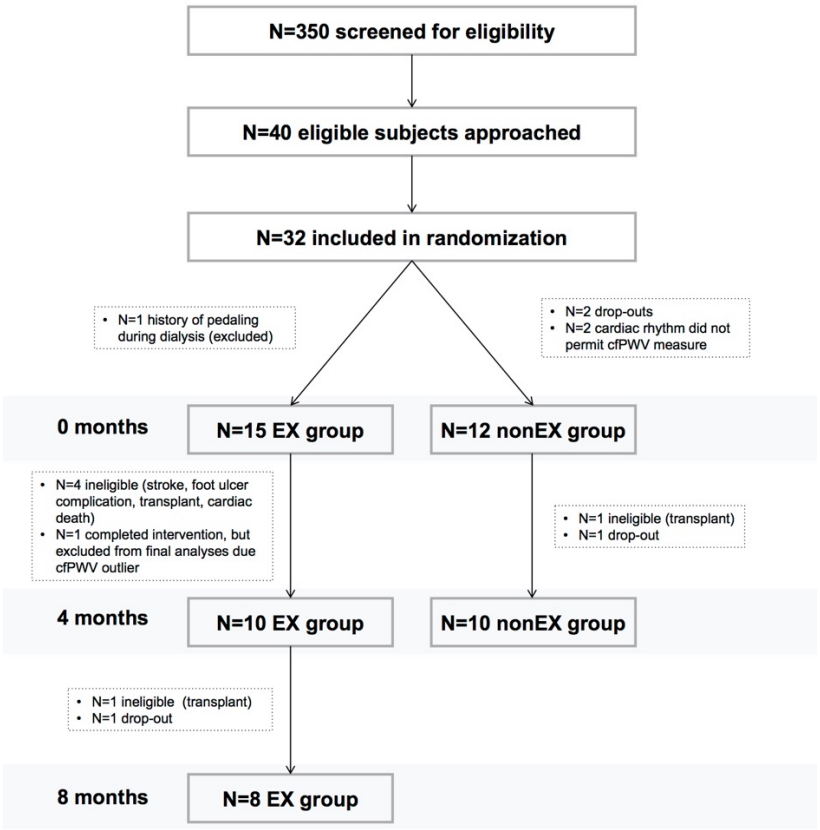
	Total Population (n=20)	Exercise Group (n=10)	Control Group (n=10)	P value
Age (years)	55.4 ± 16.2	58.2 ± 17.2	52.5 ± 15.4	0.643
Men/Women	14/6	7/3	7/3	1.00
Height (cm)	174.9 ± 8.3	172.4 ± 8.4	177.4 ± 7.9	0.168
Weight (kg)	80.9 ± 16.2	76.6 ± 16.9	85.1 ± 15.2	0.353
BMI (kg/m^2)	26.4 ± 5.2	25.6 ± 4.3	27.2 ± 6.1	0.436
Waist:hip ratio	0.94 ± 0.11	0.93 ± 0.12	0.95 ± 0.11	0.762
IPAQ (MET-min/week)	480 [0-1440]	480 [0-1440]	471 [0-1506]	0.902
Gait speed (m/s)	0.84 ± 0.27	0.8 ± 0.2	0.9 ± 0.3	0.481
Grip Strength (kg)	24.6 ± 12.0	23.2 ± 10.5	25.9 ± 13.8	0.616
Comorbidities (%)				
Coronary artery disease	10	20	0	0.136
Myocardial infarction	5	10	0	0.305
Congestive heart failure	20	20	20	1.00
Cerebrovascular accident	10	10	10	1.00
Peripheral arterial disease	5	0	10	0.304
Chronic obstructive pulmonary disease	15	20	10	0.531
Hypertension	100	100	100	1.00
Diabetes mellitus	35	30	40	0.639
Ever-smoking	45	40	50	0.653
Charlson Comorbidity Score	4.7 ± 1.7	4.6 ± 2.0	5.0 ± 1.4	0.581
Laboratory parameters				
Kt/V	1.4 ± 0.3	1.4 ± 0.3	1.5 ± 0.3	0.736
Creatinine (μmol/L)	839.7 ± 281.6	801.6 ± 244.0	877.7 ± 330.9	0.393
Hemoglobin (g/L)	107.1 ± 10.5	109.1 ± 11.1	105.1 ± 10.0	0.382
Leukocytes	6.8 ± 1.9	6.9 ± 1.9	6.6 ± 2.0	0.699
Platelets	174.6 ± 50.1	181.0 ± 35.0	168.1 ± 63.0	0.492
Albumin (g/L)	33.4 ± 4.36	32.3 ± 3.6	34.5 ± 4.9	0.269
Sodium (mmol/L)	136.2 ± 2.35	136.2 ± 3.0	136.1 ± 1.6	0.861
Potassium (mmol/L)	4.6 ± 0.6	4.5 ± 0.3	4.6 ± 0.8	0.672
Total calcium (mmol/L)	2.1 ± 0.3	2.1 ± 0.2	2.2 ± 0.3	0.323

Phosphate (mmol/L)	1.4 ± 0.4	1.5 ± 0.5	1.3 ± 0.4	0.315
PTH (pmol/L)	67.0 [23.8-93.5]	76.2 [47.0-93.5]	52.8 [23.8-67.0]	0.315
Triglycerides (mmol/L)	2.2 [1.1-2.6]	2.3 [1.2-2.6]	1.3 [0.8-2.5]	0.537
LDL (mmol/L)	2.0 ± 0.8	2.1 ± 0.9	2.0 ± 0.9	0.905
HDL (mmol/L)	1.0 ± 0.1	1.0 ± 0.1	1.0 ± 0.1	0.931
Transferrin Saturation (%)	0.3 ± 0.1	0.3 ± 0.1	0.3 ± 0.1	0.796
Ferritin (ng/mL)	463 [258.3-612.5]	471.2 [349.-683.3]	284.4 [258.4-526.0]	0.604
Medications (%)				
Anti-hypertensive agents (no.)	1.9 ± 1.2	2.45 ± 0.9	1.3 ± 1.2	0.036
ACE inhibitors or ARBs	25	30	20	0.606
Calcium channel blockers	45	50	40	0.653
Diuretics	15	30	0	0.060
β-blockers	65	90	40	0.019
α-blockers	15	20	10	0.531
Central agents	15	20	10	0.531
Nitrates	10	10	10	1.00
Acetylsalicylic acid	25	30	20	0.606
Statins	30	30	30	0.361
Phosphate binders	100	100	100	1.00
Supplemental calcium	40	60	20	0.068
Erythropoietin	90	90	90.0	1.00

Values expressed as mean ± standard deviation, median [interquartile range] or percentage.
ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; HDL, high density lipoprotein cholesterol; IPAQ, international physical activity questionnaire; LDL, low density lipoprotein cholesterol; MET, metabolic equivalent; PTH, parathyroid hormone.

Reasons for drop-out or exclusion are summarized in Figure 1.

Figure 1. Participant Flow



cfPWV, carotid femoral pulse wave velocity, EX group, exercise group; nonEX group, control group

Participant baseline characteristics including both completers and non-completers were similar (Supplementary Table 1). Of the 10 participants who completed the pedaling exercise, 8 participants were included at the 8-month follow-up.

We observed no significant between-group differences in demographic characteristics, anthropometrics, physical function, comorbidities, medications or laboratory parameters (Table 1). Furthermore, baseline vessel hemodynamics were not significantly different between the groups, with the exception of a higher aortic pulse pressure in the EX group than in the nonEX group (Table 2).

Table 2 – Baseline Arterial Stiffness and Hemodynamic Parameters

	Exercise Group (n=10)	Control Group (n=10)	P value Exercise vs. Control
Inter-dialytic weight gain (kg)	1.8 [0.5, 2.2]	2.0 [1.6, 2.4]	0.481
Peripheral SBP (mmHg)	148 [135, 166]	134 [129, 141]	0.271
Peripheral DBP (mmHg)	77 [69, 85]	83 [77, 86]	0.470
Central SBP (mmHg)	131 [122, 148]	122 [117, 126]	0.224
Central DBP (mmHg)	79 [71, 86]	85 [78, 87]	0.567
Central PP (mmHg)	53 [45, 66]	37 [32, 54]	0.045
MAP (mmHg)	98 [91, 110]	101 [93, 103]	0.984
cfPWV (m/s)	8.2 [7.3, 9.8]	8.6 [7.2, 9.2]	0.739
HR (bpm)	67 [60, 81]	75 [69, 78]	0.315
AIx75 (%)	24 [19, 26]	22 [15, 28]	0.448

Values expressed as median [interquartile range]
Bolded values indicate significance ($P<0.05$)
AIx75, Augmentation index (corrected for a heart rate of 75 beats/min); cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP systolic blood pressure

A higher pulse pressure was also noted in the EX group when non-completers were also included (Supplementary Table 2). Changes in the number and dose of medications was minimal; one EX group participant received a dose increase of an antihypertensive agent (clonidine), and a nonEX participant started a calcimimetic agent and received an increased dose of an angiotensin receptor blocker.

Exercise Compliance

Median exercise compliance in the EX group was 60% [IQR 42-79] and median exercise time per session was 42.6 minutes [IQR 31.2-60.0]. Over the intervention, the median total exercise time was 18.5 hours [IQR 10.5-28.5] per participant.

Safety and Adverse Events

No adverse events occurred during exercise. Two withdrawals from the exercise intervention were due to health complications, unrelated to the exercise. One participant withdrew for cardiac bypass surgery, and subsequent post-operative complications led to death; however, this was not related to the exercise. There was one case of ischemic stroke, but the episode occurred 10 days after cessation from the exercise program.

Post-Intervention Changes

Vessel Hemodynamics

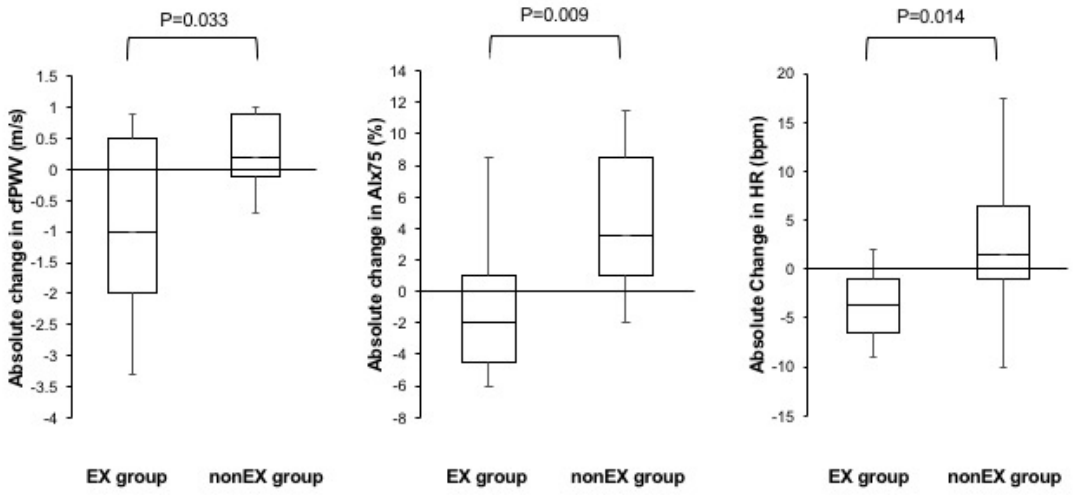
Peripheral and central BP were unchanged after the intervention in both the EX and nonEX groups (Table 3). We observed a significantly greater absolute decrease in cfPWV in the EX group compared to the nonEX group (*P=0.033*): -1.00 [IQR -1.95, 0.05] vs. 0.20 [IQR -0.10, 0.9] (Figure 2). Furthermore, AIx75 was unchanged in the EX group, however a significant median increase of 3.5% (IQR 1.0, 8.5) was noted in the nonEX group (between-group *P=0.009*). We also noted a greater reduction in HR in the EX group post-intervention, compared to the nonEX group (*P=0.029*).

Table 3 – Between-group Comparisons of Post-exercise Changes in Arterial Stiffness and Hemodynamic Parameters

	Exercise Group (n=10)	Control Group (n=10)	P value Exercise vs. Control	P value Exercise Post vs. Pre	P value Control Post vs. Pre
Δ BMI (kg/m²)	0.28 [-0.23, 0.95]	0.20 [-0.03, 0.45]	0.485	0.359	0.106
Δ Waist:hip ratio	0.03 [0.01, 0.03]	-0.00 [-0.03, 0.01]	0.022	0.065	0.313
Δ Inter-dialytic weight gain (kg)	-0.6 [-0.6, 1.1]	-0.1 [-0.6, 0.9]	0.309	0.607	0.844
Δ Gait speed (m/s)	0.02 [-0.02, 0.11]	-0.11 [-0.17, 0.08]	0.158	0.557	0.275
Δ Grip strength (kg)	1.3 [-0.5, 6.5]	2.5 [-0.5, 4.0]	0.464	0.176	0.050
Δ Peripheral SBP (mmHg)	-10.0 [-21.5, 4.0]	-0.3 [-5.0, 6.5]	0.128	0.106	0.969
Δ Peripheral DBP (mmHg)	-5.3 [-11.0, 8.5]	0.5 [-1.0, 11]	0.092	0.320	0.607
Δ Central SBP (mmHg)	-10.0 [-16.0, 3.5]	1.0 [-2.5, 11.5]	0.099	0.152	0.770
Δ Central DBP (mmHg)	-6.0 [-10, 6.0]	-2.0 [-1.0, 12.0]	0.136	0.203	0.420
Δ Central PP (mmHg)	-6.5 [-9.5, 6.0]	-3.3 [-4.5, 6.0]	0.105	0.186	0.977
Δ MAP (mmHg)	-9.0 [-15.0, 4.0]	2.0 [-1.5, 9.5]	0.162	0.125	0.422
Δ cfPWV (m/s)	-1.0 [-2.0, 0.5]	0.20 [-0.1, 0.9]	0.033	0.160	0.170
Δ AIx75 (%)	-2.0 [-4.5, 1.0]	3.5 [1.0, 8.5]	0.009	0.361	0.023
Δ HR (bpm)	-3.8 [-6.5, -1.0]	1.5 [-1.0, 6.5]	0.014	0.020	0.361

Values expressed as median [interquartile range]
Δ indicates absolute difference (post minus pre intervention levels)
Bolded values indicate significance ($P<0.05$)
AIx75, augmentation index (corrected for a heart rate of 75 beats/min); BMI, body mass index; cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

Figure 2. Absolute Change from Baseline in cfPWV, AIx75 and Heart Rate at 4 Months



AIx75, augmentation index corrected for a heart rate of 75 beats/min; cfPWV, carotid femoral pulse wave velocity; HR, heart rate

To account for the small size of our pilot randomized controlled trial and possible imbalances in characteristics due to drop-outs after randomization, we performed additional adjusted analyses for potential confounding variables. In three separate models after adjustments for two potential confounders, age and the Charlson comorbidity score, as well as the baseline cfPWV value, the decrease in cfPWV approached significance in the EX group (model 1: age, baseline cfPWV value, *P=0.055;* model 2: Charlson comorbidity score and baseline cfPWV value, *P=0.059*; model 3: age, Charlson comorbidity score, and baseline cfPWV value *P=0.067*). Due to considerable skewness, normality could not be achieved with data transformations for AIx75 or HR, preventing adjusted analyses for these parameters.

In a single-arm secondary analysis that included 5 additional control arm participants who subsequently underwent the exercise intervention (total n=15), we also found a

significant lowering of cfPWV by -0.96±1.32 m/s (95% CI -1.7 to -0.23, *P=0.014*). No conclusive changes were noted for the other hemodynamic parameters (Supplementary Table 3).

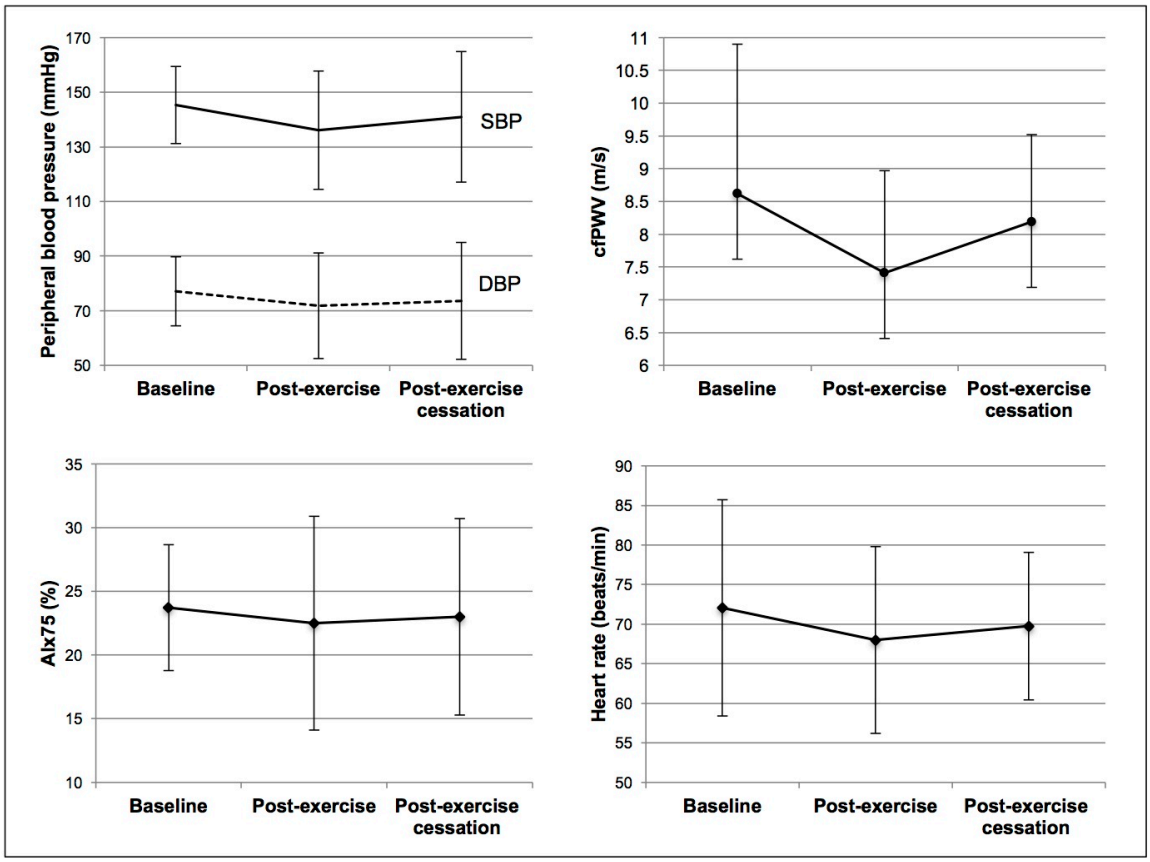
Physical Function and Laboratory Parameters

Post-intervention changes in gait speed and grip strength were minimal and were not significantly different between EX and nonEX participants (Table 3). We did not observe any between-group differences in any of the laboratory blood markers in either group over the intervention period (data not shown).

Post-exercise Cessation Follow-Up

cfPWV at the follow-up evaluation in the EX group (mean±SD: 8.2±1.3 m/s, 95% CI 7.1 to 9.3) was intermediate between the baseline (8.6±2.3 m/s, 95% CI 6.7 to 10.4) and post-intervention values (7.4±1.6 m/s, 95% CI 6.2 to 8.6) (Figure 3). We noted a similar observation for an intermediate value at 8 months for peripheral BP and pulse pressure, HR, and AIx75 (Figure 3). Data for all parameters is displayed in Supplementary Table 4.

Figure 3. Exercise Group: cfPWV and Other Hemodynamic Parameters at Baseline, Post-exercise and 4 Months After Exercise Cessation



AIx75, augmentation index corrected for a heart rate of 75 beats/min; cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; SBP, systolic blood pressure.

5.2.5 Discussion

This pilot study demonstrated that intradialytic pedaling exercise leads to a significant improvement in cfPWV, the "gold standard" measurement of arterial stiffness. Importantly, the magnitude of this reduction (-1 m/s) is considered clinically relevant; a 1 m/s increase in cfPWV is associated with a 15% increased risk of cardiovascular events, and mortality[17]. Specifically in hemodialysis patients, a 1 m/s increase in cfPWV corresponds to a 39% increased risk in all-cause mortality (adjusted relative risk 1.39, 95% CI 1.19 to 1.62)[3]. Interestingly, the improvement in cfPWV after pedaling exercise was observed in the absence of significant changes in BP, physical function, body mass index, or lipids. Our secondary analyses further support the beneficial impact of intradialytic pedaling on cfPWV. In a single-arm subgroup analysis that included 5 additional participants who performed the pedaling intervention, we demonstrated a significant decrease in cfPWV of similar magnitude (-0.96 m/s). We also demonstrated that exercise cessation leads to a partial reversal of cfPWV 4 months later. Although pedaling exercise did not significantly change AIx75, a surrogate measure of systemic stiffness, we noted a significant median increase of 3.5% in the control group. Interestingly, we observed significantly lower resting HR in response to 4 months of pedaling.

Few studies have examined the arterial health impact of aerobic exercise[12,18,19]. Among them, Mustata et al. found an improvement in AIx after 3 months of supervised aerobic exercise using a treadmill or recumbent bike (two sessions of 60 minutes/week) in 11 hemodialysis patients at a cardiac rehabilitation centre[12]. More recently, they found similar reductions in AIx in response to supervised and home exercise (3 sessions of 60 minutes/week) in 20 pre-dialysis patients[19]. Although both interventions have

demonstrated improvements in AIx, supervised aerobic exercise programs requiring specialized equipment are resource intensive and difficult to maintain in the longer-term.

Intradialytic exercise has the advantage of being performed in a supervised setting, requires no additional time commitment outside of dialysis, and is considered feasible for the many hemodialysis patients with functional limitations that would prevent more rigorous forms of aerobic exercise[20]. As such, it has been proposed as a realistic means to help patients achieve the arterial health benefits of increased physical activity; however, the results to date have been inconclusive. Our study is the first to show important promise for arterial health benefit by significantly lowering cfPWV. These findings support those of Toussaint et al. who observed a decrease in cfPWV after 3 months of intradialytic pedaling exercise (n=9) that approached significance (P=0.07); however they did not compare the cfPWV change in response to exercise between those who exercised versus controls[21]. Although non-significant, Koh et al. observed a -0.8 (95% CI, -2.11 to 0.48) difference in cfPWV after 6 months of intradialytic pedaling (n=15) versus usual care (n=15)[11]. Although we have shown a significant increase in AIx75 in the nonEX group compared to the EX group, neither of these studies[11,21] observed a difference in AIx75 after intradialytic pedaling. Furthermore, we observed a modest, but significant decrease in HR of 3.7 beats/min. Ouzouni et al. reported an even larger decrease in HR of 8.7 beats/min after 10 months of intradialytic pedaling (n=19)[22]. Therefore, further benefit with a longer-term intervention is possible.

In order to evaluate the sustainability of the pedaling effect we performed an additional evaluation in the exercise group 4 months post-intervention. Interestingly, cfPWV at the follow-up evaluation was intermediate between the baseline and post-intervention value, suggestive of a possible carry-over effect of arterial stiffness. This is in contrast to a previous study by Mustafa et al. which showed that AIx improvements

after pedaling dissipated after 1 month of detraining[12]. Toussaint et al. reported an almost complete return to baseline 4 months after exercise cessation, [21]. A more rigorous examination of the sustainability of this effect will be required in a much larger number of patients to draw definite conclusions; however, the current evidence demonstrating either a partial or complete reversal of the effect emphasizes the need for maintenance of regular physical activity in this population.

Exercise improves arterial stiffness through several mechanisms, including functional and structural improvements in the central conduit arteries. Even short-term mild intensity cycling exercise has been shown to have favorable effects on the endothelium by improving nitric oxide bioavailability[18,23-26]. Interestingly, a 16-week intervention consisting of treadmill walking (50-60% VO_2 peak) in patients with stage 3 CKD led to improvements in vasoactive balance, as demonstrated by a higher nitrate/nitrite to endothelin-1 ratio[18]. Furthermore, the observed reduction in HR suggests that the pedaling exercise may have improved autonomic control[27]. This could in turn reduce sympathetic activation of vascular smooth muscle cells and may be a possible mechanism for lower arterial stiffness[28]. The carry-over effect of exercise on cfPWV 4 months post-exercise cessation is perhaps also indicative of structural improvements. Exercise may have impacted the concentrations of collagen, or the cross-linking of structural proteins by advanced glycation end-products within the arterial wall, both key contributors to arterial stiffness[23]. Although we have not measured the levels of inflammatory markers other than leukocytes and platelets, exercise exerts important anti-inflammatory effects. Numerous studies have demonstrated a strong association between inflammatory markers and cfPWV[29].

Study limitations include a small sample size and relatively short intervention duration. Despite all efforts, renal transplants and health-related contraindications for

exercise led to several drop-outs. Other longitudinal studies investigating intradialytic pedaling have faced similar limitations[11,18,19,21,30,31]. Furthermore, we adjusted cfPWV, our primary outcome, for the value at baseline, as well as variables that correlated strongly with cfPWV (age and Charlson comorbidity score), despite no significant differences at baseline. We have included several secondary outcomes to contextualize our results; however, we caution readers to consider the fact that multiple testing was conducted. While the study was originally designed as a cross-over study, hospital logistics did not permit a wash-out period. Therefore, we have presented the results as a RCT with a 4-month follow-up. However, this provided control arm participants with the opportunity to engage in the pedaling exercise protocol after completing the first 4-month intervention period. This additional step allowed us to conduct a single-arm subgroup analysis in a larger number of participants and further confirm the beneficial impact of pedaling exercise on cfPWV. Exercise compliance was variable (60% [IQR 42-79]). We discouraged participants from pedaling if they were not feeling well, which led to a lower compliance rate than expected[32]. Moreover, non-availability of volunteers delegated to supervise the exercise sessions also impacted participant compliance. We elected to not involve research staff for supervision of exercise sessions in order to evaluate the impact of a more 'real life' intervention integrated into the dialysis unit. Lastly, the available pedaling equipment did not enable us to measure the intensity of pedaling. However, participants aimed to reach the target range on the Borg RPE Scale[20].

In conclusion, intradialytic exercise has been increasingly recognized as a safe and effective modality that allows patients to integrate regular physical activity into their hemodialysis sessions. Despite a small sample size and the relatively short exercise duration, we demonstrated a clinically relevant reduction in cfPWV, the "gold-standard" measure of arterial stiffness. The benefit is only partially sustained soon after exercise

cessation, and therefore reinforces the need for maintenance of regular physical activity in this population to achieve arterial health benefits. These findings need to be confirmed in larger future investigations with longer duration of exercise regimens.

5.2.6 Acknowledgements

We acknowledge MUHC dialysis unit staff members and volunteers, whose help was instrumental in executing this study.

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5.2.7 Conflicts of Interest

None.

5.2.7 References

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5.3 Supplemental Material – Manuscript 3

Supplementary Table 1 – Baseline characteristics in all participants assessed at baseline (completers and non-completers)

	Exercise Group (n=15)	Control Group (n=12)	P value
Age (years)	59.5 ± 16.2	52.8 ± 14.4	0.392
Men/Women	10/5	8/4	1.000
Height (cm)	169.4 ± 9.1	174.5 ± 9.9	0.162
Weight (kg)	77.8 ± 18.3	87.5 ± 13.8	0.222
BMI (kg/m^2)	26.7 ± 5.4	28.5 ± 6.3	0.347
Waist:hip ratio	0.94 ± 0.11	0.93 ± 0.12	0.891
Gait speed (m/s)	0.8 ± 0.3	0.9 ± 0.3	0.283
Grip Strength (kg)	21.6 ± 10.3	25.4 ± 12.8	0.478
Comorbidities (%)			
Coronary artery disease	33	0	0.027
Myocardial infarction	20	0	0.100
Congestive heart failure	20	17	0.825
Cerebrovascular accident	20	8	0.397
Peripheral arterial disease	7	8	0.870
Chronic obstructive pulmonary disease	20	8	0.397
Hypertension	100	100	1.000
Diabetes mellitus	40	33	0.722
Ever-smoking	60	50	0.603
Charlson Comorbidity Score	4.9 ± 2.3	4.8 ± 1.3	0.953
Laboratory parameters			
Kt/V	1.4 ± 0.3	1.5 ± 0.3	0.888
Hemoglobin (g/L)	106.9 ± 12.6	105.8 ± 9.6	0.838
Leukocytes	7.3 ± 1.9	7.1 ± 2.2	0.991
Platelets	187.5 ± 39.0	169.3 ± 57.1	0.204
Albumin (g/L)	32.5 ± 3.2	34.3 ± 4.7	0.303
Sodium (mmol/L)	136.7 ± 3.2	136.0 ± 1.8	0.403
Potassium (mmol/L)	4.7 ± 0.5	4.7 ± 0.8	0.819
Total calcium (mmol/L)	2.1 ± 0.2	2.2 ± 0.3	0.556
Phosphate (mmol/L)	1.5 ± 0.5	1.3 ± 0.4	0.683
PTH (pmol/L)	76.2 [38.6, 93.5]	51.7 [23.5-67.0]	0.202
Triglycerides (mmol/L)	2.3 [1.2-2.7]	1.3 [0.8-2.5]	0.524
LDL (mmol/L)	1.8 ± 0.8	2.0 ± 0.9	1.000
HDL (mmol/L)	1.1 ± 0.1	1.0 ± 0.1	0.833
Transferrin Saturation (%)	0.3 ± 0.1	0.2 ± 0.1	0.249
Ferritin (ng/mL)	501.7 [349.-683.3]	482.9 [258.3-605.1]	0.809
Medications (%)			
Anti-hypertensive agents (no.)	2.3 ± 1.0	1.3 ± 1.1	0.026

ACE inhibitors or ARBs	33	17	0.326
Calcium channel blockers	47	42	0.795
Diuretics	27	8	0.223
β-blockers	87	33	0.004
α-blockers	13	8	0.681
Central agents	13	8	0.681
Nitrates	20	8	0.397
Acetylsalicylic acid	40	17	0.187
Statins	53	33	0.299
Phosphate binders	100	100	1.000
Supplemental calcium	47	17	0.100
Erythropoietin	93	83	0.411

Values expressed as mean ± standard deviation, median [interquartile range] or percentage.
ACE, angiotensin converting enzyme; ARBs, angiotensin receptor blockers; BMI, body mass index; HDL, high density lipoprotein cholesterol; IPAQ, international physical activity questionnaire; LDL, low density lipoprotein cholesterol; PTH, parathyroid hormone.

Supplementary Table 2 - Arterial stiffness and hemodynamic parameters in all participants assessed at baseline (completers and non-completers)

	Exercise Group (n=15)	**Control Group (n=12)**	**P value Exercise vs. Control**
Inter-dialytic weight gain (kg)	1.5 [0.5, 2.2]	2.0 [1.7, 2.5]	0.141
Peripheral SBP (mmHg)	146 [135, 166]	133 [130, 139]	0.116
Peripheral DBP (mmHg)	73 [65, 85]	83 [79, 86]	0.163
Central SBP (mmHg)	126 [122, 148]	122 [117, 126]	0.135
Central DBP (mmHg)	74 [66, 86]	85 [80, 88]	0.195
Central PP (mmHg)	55 [45, 70]	37 [31, 48]	0.003
MAP (mmHg)	93 [88, 110]	101 [93, 104]	0.462
cfPWV (m/s)	7.9 [7.4, 9.8]	8.7 [7.6, 9.3]	1.000
HR (bpm)	66 [59, 74]	75 [69, 82]	0.087
AIx75 (%)	23 [19, 26]	23 [15, 28]	0.764

Values expressed as median [interquartile range]
Bolded values indicate significance ($P<0.05$)
AIx75, augmentation index (corrected for a heart rate of 75 beats/min); cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure

Supplementary Table 3 – Arterial stiffness and hemodynamic parameters in response to pedaling exercise and 4 months after exercise cessation

	Baseline (0 month, n=8)	Post-Exercise (4 month, n=8)	Post-Exercise Cessation (8 month, n=8)	P-value
Peripheral SBP	146 (134, 156)	136 (120, 153)	141 (123, 159)	0.583
Peripheral DBP	77 (67, 87)	72 (66, 77)	74 (64, 83)	0.708
Central SBP	132 (122, 141)	124 (109, 139)	129 (112, 145)	0.594
Central DBP	79 (68, 89)	73 (68, 79)	74 (65, 84)	0.697
Central PP	53 (42, 64)	50 (37, 64)	55 (40, 69)	0.883
MAP	100 (90, 109)	93 (85, 101)	96 (84, 107)	0.671
cfPWV	8.6 (6.9, 10.4)	7.4 (6.2, 8.6)	8.2 (7.1, 9.3)	0.463
AIx75	24 (20, 28)	23 (16, 29)	23 (17, 29)	0.862
HR	72 (62, 83)	68 (59, 77)	70 (62, 78)	0.878

Values expressed as mean (95% confidence interval)
AIx75, augmentation index (corrected for a heart rate of 75 beats/min); BMI, body mass index; cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure

Supplementary Table 4 – Arterial stiffness and hemodynamic parameters in response to pedaling exercise (single-arm subgroup analysis in 15 participants)

	Baseline (0 month, n=15)	Post-Exercise (4 month, n=15)	Absolute Change (Post-Pre)
Peripheral SBP	144.40 (135.02, 153.78)	138.77 (125.48, 152.06)	-5.63 (-13.41, 2.14)
Peripheral DBP	79.00 (72.81, 85.19)	75.80 (70.50, 81.10)	-3.20 (-7.9, 1.50)
Central SBP	130.67 (123.09, 138.25)	125.60 (114.07, 137.13)	-5.07 (-12.34, 2.21)
Central DBP	80.57 (74.16, 86.98)	77.30 (71.89, 82.71)	-3.27 (-8.07, 1.54)
Central PP	50.10 (42.32, 57.88)	48.30 (30.28, 57.32)	-1.8 (-6.57, 2.97)
MAP	101.07 (94.70, 107.44)	97.00 (89.37, 104.63)	-4.07 (-9.80, 1.67)
cfPWV	8.89 (7.86, 9.93)	7.93 (7.06, 8.80)	-0.96 (-1.70, -0.23)
AIx75	24.40 (21.52, 27.28)	23.67 (19.84, 27.49)	-0.73 (-3.30, 1.83)
HR	73.23 (66.86, 79.60)	72.00 (65.41, 78.59)	-1.23 (-4.89, 2.42)

Values expressed as mean (95% confidence interval)
AIx75, Augmentation index (corrected for a heart rate of 75 beats/min); BMI, body mass index; cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure

Supplementary Table 5 – Between-group and Within-group Comparisons of Changes in Arterial Stiffness and Hemodynamic Parameters

	Exercise Group (n=10)	Control Group (n=10)	P value Exercise vs. Control	P value Exercise Post vs. Pre	P value Control Post vs. Pre
Δ BMI (kg/m^2)	0.28 [-0.23, 0.95]	0.20 [-0.03, 0.45]	0.485	0.359	0.106
Δ Waist:hip ratio	0.03 [0.01, 0.03]	-0.00 [-0.03, 0.01]	0.022	0.065	0.313
Δ Inter-dialytic weight gain (kg)	-0.6 [-0.6, 1.1]	-0.1 [-0.6, 0.9]	0.309	0.607	0.844
Δ Gait speed (m/s)	0.02 [-0.02, 0.11]	-0.11 [-0.17, 0.08]	0.158	0.557	0.275
Δ Grip strength (kg)	1.3 [-0.5, 6.5]	2.5 [-0.5, 4.0]	0.464	0.176	0.050
Δ Peripheral SBP (mmHg)	-10.0 [-21.5, 4.0]	-0.3 [-5.0, 6.5]	0.128	0.106	0.969
Δ Peripheral DBP (mmHg)	-5.3 [-11.0, 8.5]	0.5 [-1.0, 11]	0.092	0.320	0.607
Δ Central SBP (mmHg)	-10.0 [-16.0, 3.5]	1.0 [-2.5, 11.5]	0.099	0.152	0.770
Δ Central DBP (mmHg)	-6.0 [-10, 6.0]	-2.0 [-1.0, 12.0]	0.136	0.203	0.420
Δ Central PP (mmHg)	-6.5 [-9.5, 6.0]	-3.3 [-4.5, 6.0]	0.105	0.186	0.977
Δ MAP (mmHg)	-9.0 [-15.0, 4.0]	2.0 [-1.5, 9.5]	0.162	0.125	0.422
Δ cfPWV (m/s)	-1.0 [-2.0, 0.5]	0.20 [-0.1, 0.9]	0.033	0.160	0.170
Δ AIx75 (%)	-2.0 [-4.5, 1.0]	3.5 [1.0, 8.5]	0.009	0.361	0.023
Δ HR (bpm)	-3.8 [-6.5, -1.0]	1.5 [-1.0, 6.5]	0.014	0.020	0.361

Values expressed as median [interquartile range]
Δ indicates absolute difference (post minus pre intervention levels)
Bolded values indicate significance (P<0.05)
AIx75, augmentation index (corrected for a heart rate of 75 beats/min); BMI, body mass index; cfPWV, carotid femoral pulse wave velocity; DBP, diastolic blood pressure; HR, heart rate; MAP, mean arterial pressure; SBP, systolic blood pressure.

5.4 Additional Analyses for Manuscript 3

Part 1

Since publication of our manuscript, we carried out additional analyses, where linear regression models were used to evaluate differences in arterial stiffness and hemodynamics between the exercise (EX) and control (nonEX) groups. The post-intervention value at 4 months was modelled as the dependent variable, which was adjusted for the pre-intervention value. Group (EX vs. nonEX) was also included as an independent variable, thus allowing us to capture the between-group difference in the response of arterial stiffness and hemodynamics to the intervention. The model was as follows: *Post-intervention value = pre-intervention value + group*. Additionally, relevant covariates were included as independent variables in the model. A similar approach was applied in *Manuscript 4*.

The pre- and post-intervention values for each of the variables were normally distributed. However, the change in many of these variables, including cfPWV (main outcome) was not. This new approach does not require us to use the change in cfPWV and allowed us to apply linear regression models without the need for transformations (as we originally did in our published manuscript).

We also evaluated aortic stiffness β_0, a novel blood pressure independent measure of arterial stiffness. The calculation of aortic stiffness β_0 adjusts cfPWV for the diastolic blood pressure at the time of measurement, and does not require statistical adjustment for blood pressure. We considered this measure in *Manuscript 4* when assessing the response of arterial stiffness to acute maximal exercise in adults with and without T2DM; however, this measure was only developed after the publication of *Manuscript 3*.

As shown in the table below, the intradialytic pedaling exercise had conclusive effects on cfPWV, aortic stiffness β_0, AIx75 and HR.

Additional Table 1. Between-group difference in unadjusted arterial stiffness and hemodynamic parameters

	Mean Difference (95% CI) (Exercise – Control)
Peripheral SBP (mmHg)	-4.1 (-20.3, 12.0)
Peripheral DBP (mmHg)	-5.8 (-15.2, 3.5)
Peripheral PP (mmHg)	-5.2 (-13.1, 2.8)
Central SBP (mmHg)	-1.1 (-17.0, 14.9)
Central DBP (mmHg)	-6.1 (-15.2, 3.0)
Central PP (mmHg)	-2.3 (-10.1, 5.5)
MAP (mmHg)	-4.9 (-16.1, 6.3)
cfPWV (m/s)	**-1.12 (-2.14, -0.1)**
Aortic stiffness β_0	**-2.9 (-5.7, -0.1)**
AIx75 (%)	**-5.0 (-9.6, -0.4)**
HR (bpm)	**-7.1 (-13.3, -0.9)**

Importantly, the conclusive between-group difference in cfPWV, our main outcome, persisted after adjusting for relevant covariates (each added separately): delta MAP (-1.00 m/s [95% CI -1.97, -0.01]), age (-1.12 m/s [95% CI -2.20, -0.06]), Charlson Comorbidity score (-1.13 m/s [95% CI -2.22, -0.04]), baseline PP (-1.53 m/s [95% CI -2.61, -0.44]). Similarly, the improvement in aortic stiffness β_0, persisted when adjusting for both age and the Charlson Comorbidity score (-3.19 [95% -6.35, -0.02]).

Part 2

We performed additional analyses that included the 5 participants who dropped out from the exercise intervention. Our previously published analyses excluded these participants because we did not have arterial stiffness measurements at the 4-month timepoint. In the revised analyses, their baseline value was carried forward, which is a conservative approach. Between-group differences in the response of cfPWV, aortic stiffness β_0, AIx75 and HR remained significant:

cfPWV: -0.94 m/s (95% CI -1.75, -0.14)

Aortic stiffness β_0: -2.87 (95% CI -5.66, -0.07)

AIx75: -4.12 % (95% CI -7.54, -0.69)

HR: -6.10 bpm (95% CI -11.15, -1.00)

CHAPTER 6:

Arterial Stiffness and Blood Pressure Response to Acute Maximal Exercise in Adults with and without Type 2 Diabetes Mellitus

6.1 Preamble – Manuscript 4

It is well understood that aerobic exercise has the potential to reduce arterial stiffness[24]. Higher intensities of aerobic exercise have been shown to lead to greater improvements[24]; however, high-intensity aerobic exercise is not realistic for many individuals with ESRD. The PEDAL trial demonstrated that a more realistic form of low-intensity aerobic exercise integrated into dialysis sessions can elicit improvements in arterial health. I have also been interested in the effects of acute exercise on arterial stiffness. I co-authored a systematic review that evaluated the impact of acute aerobic exercise on immediate changes in arterial stiffness[186]. We concluded that the response of arterial stiffness was dependent on the anatomical segment studied, as well as the timing of the measurement. When assessing central artery stiffness, the majority of studies reported a significant increase immediately post-exercise. While this initial increase is considered to be a normal adaptation to exercise, the degree to which arterial stiffness increases may reflect the ability of the arteries to respond to increased demands.

Individuals with T2DM are known to have an exaggerated blood pressure response to acute exercise. Reviews on the topic of 'exercise hypertension' mention large artery stiffness as a possible mechanism; however, this had previously not been investigated in the context of maximal exercise. In SMARTER, participants completed the 'arterial stress test' which involves measures of arterial stiffness before and immediately after acute maximal exercise. This provided me with the opportunity to explore the arterial stiffness response to acute maximal exercise in individuals with and without T2DM. This work was published in *Hypertension* on April 27, 2020.

6.2 Content – Manuscript 4

Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics

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6.2.1 Abstract

Individuals with type 2 diabetes mellitus (T2DM) have a greater blood pressure (BP) response to acute maximal exercise compared to those without T2DM; however, whether they exhibit a different arterial stiffness (AS) response to maximal exercise has yet to be explored. Adults with (n=66) and without T2DM (n=61) underwent an 'arterial stress test': at rest and immediately post-exercise, carotid-femoral pulse wave velocity (cfPWV), the gold-standard measure of AS, brachial BP, heart rate (HR) and other hemodynamic measurements were assessed. Linear regression models were used to evaluate between-group differences at rest, and the response to exercise (post-exercise value), adjusting for covariates including BP and HR when relevant, and the corresponding baseline value of each parameter. All participants (mean±SD: age 59.3±10.6 years; BMI 31.2±3.9 kg/m^2) had hypertension (mean BP 130±14/80±9 mmHg). At rest, participants with T2DM had

significantly higher cfPWV (10.3±2.7 vs. 9.1±1.9 m/s), HR (69±11 vs. 66±10 beats/min), and lower DBP (79±9 vs. 83±9 mmHg), but SBP (129±15 vs. 131±13 mmHg) was similar. In response to exercise, participants with T2DM showed greater increases in cfPWV (1.6, 95% CI 0.4, 2.9 m/s), and SBP (9, 95% CI 1, 17 mmHg) than participants without T2DM. A greater proportion of participants with T2DM had a hypertensive response to exercise compared to participants without T2DM (n=23, 35% vs. n=11, 18%) (P=0.033). By incorporating exercise as a vascular stressor, we provide evidence of a greater increase in AS in individuals with T2DM, independently of resting AS, and the BP post-exercise.

6.2.2 Introduction

Type 2 diabetes mellitus (T2DM) increases arterial stiffness through pathological changes in the vasculature, including reduced nitric oxide bioavailability, increased oxidative stress and inflammation, as well as structural changes within the arterial wall[1]. As a result, for many individuals with T2DM, their vascular "age" surpasses their chronological age[2]. Furthermore, during maximal exercise, individuals with T2DM are more likely to experience an exaggerated blood pressure (BP) response[3]; this is defined as a rise in systolic BP (SBP) exceeding 210 mmHg in men and 190 mmHg in women and is associated with higher cardiovascular disease (CVD) risk and mortality[4]. The physiological changes underlying this altered response have not been fully elucidated, but underlying vascular abnormalities are thought to play a pivotal role[5]. However, whether individuals with T2DM have a different arterial stiffness response to exercise, independent of the resting value, has yet to be explored. In this context, increased demands associated with acute exercise might exaggerate vascular abnormalities present in these individuals.

The 'gold standard' metric for assessing arterial stiffness non-invasively is carotid-femoral pulse wave velocity (cfPWV), a measure of the speed of the pressure pulse wave in the central elastic arteries[6]. Higher values of cfPWV indicate greater arterial stiffness, which is associated with a greater risk of CVD events and mortality[7,8].

With increased metabolic demands during acute exercise, the vascular system plays an important role in the redistribution of blood flow to ensure adequate perfusion of the exercising muscle[9]. This leads to a transient increase in mean arterial pressure, sympathetic activity, and vascular tone, as well as central arterial stiffness[9]. During the recovery period, arterial stiffness has been shown to decrease to a level at, or below resting values[9]. While the initial increase in arterial stiffness is recognized as a normal adaptation to acute exercise, the extent of the increase in arterial stiffness and recovery trajectory may reflect the ability of the arteries to respond to increased demands.

In the present study, we aimed to examine the acute response of arterial stiffness and hemodynamic parameters to maximal exercise in adults with and without T2DM. We hypothesized that individuals with T2DM would have a higher arterial stiffness in response to exercise, independently of the resting values and BP.

6.2.3 Methods

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approval

The study was approved by the ethics review board of McGill University Faculty of Medicine. Written informed consent was obtained from all participants.

Study Cohort

Participants were recruited through McGill-affiliated clinics for the SMARTER trial, a one-year randomized controlled trial examining the impact of step count prescriptions on arterial health[10]. All participants of the trial were overweight or obese (body mass index 25-40 kg/m^2), had T2DM and/or hypertension, and did not have any gait abnormalities preventing exercise. Hypertension and T2DM were diagnosed by the referring physician following Canadian guidelines[11,12]. The analyses herein were conducted in hypertensive participants with and without T2DM who underwent the 'arterial stress test' at the baseline evaluation.

Exercise Testing

All participants underwent a maximal exercise test to exhaustion on a treadmill following a modified Bruce protocol[13]. Peak oxygen consumption (VO_2 peak) was obtained using a metabolic cart (Medisoft's Ergocard, Sorinne, Belgium). To ensure all participants had achieved exhaustion, participants who did not attain age-based cut-offs for the respiratory exchange ratio (RER) were excluded (aged 20-49: RER≥1.10; aged 50-64: RER≥1.05; aged ≥65: RER≥1.00)[14]. Peak heart rate (HR) was obtained using the 3-lead electrocardiogram (ECG) connected to the metabolic cart but was not used as a criterion to establish maximal effort due to the influence of β-blockers on the HR response to exercise.

Arterial Stiffness and Hemodynamics

All measurements were performed in the morning to avoid circadian rhythm variations[15,16]. Participants fasted for 12 hours prior to the assessment, and abstained from caffeine, alcohol, and smoking. Participants were offered a small healthy snack after the blood draw and prior to the 'arterial stress test' to prevent hypoglycemia and because a

fasted state could have prevented participants from exerting themselves fully. Participants avoided exercise for 24 hours prior to the assessment. All usual medications, except anti-hyperglycemic agents, were taken the morning of assessment.

Brachial BP was measured using an automated oscillometric BP monitor (BpTRU, Medical Devices Ltd, BC, Canada) in a seated position at rest[12], as well as in a supine position at rest and after exercise (at 3, 5, 10, 15 and 20 minutes), following the cfPWV measurement. MAP was calculated as: brachial diastolic BP (DBP) + 1/3 (brachial SBP-DBP)[17]. Due to the impact of body position on BP, brachial BP was assessed in the supine position in order to calibrate the central hemodynamic measures obtained in a supine position. Standing measurements of brachial BP were obtained manually using the auscultatory method immediately before and after exercise (0 minutes). This measure was used to evaluate whether participants experienced a hypertensive response to exercise, which was defined as a brachial SBP >210 mmHg in men and >190 mmHg in women[4].

Arterial stiffness, central BP, and augmentation index (AIx) were measured using applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia) in a supine position before and immediately after exercise following a standardized protocol in a controlled environment at the Vascular Health Unit at the McGill University Health Centre. Baseline measurements were obtained after a 10-minute rest period. Following exercise completion, participants returned to a supine position for the measurement of cfPWV (at 3, 5, 10, 15, and 20 minutes) and carotid-radial PWV (crPWV), central BP and AIx (at 5, 10, 15, and 20 minutes). As per SphygmoCor recommendations, the radial pressure waveforms were calibrated using brachial SBP and DBP. As calibration with MAP and DBP has been increasingly suggested[18], we also performed this analysis. HR was acquired at the same time as the cfPWV measurement using the built-in 3-lead ECG.

To account for the influence of HR on wave reflection, AIx was corrected for a HR of 75 beats/minute (AIx75). Path length was estimated using the subtraction method, whereby the distance between the carotid artery site and the sternal notch was subtracted from the distance between the sternal notch and the femoral artery site[6]. At rest, measurements were repeated until two PWV measurements were within 0.5 m/s, and two augmentation pressures were within 4%. PWA measurements with an operator index <80 and PWV measurements with a pulse transit time standard deviation >13% or HR difference >5 beats/min between sites were deemed poor quality and not considered. Due to time restrictions post-exercise, only one good quality measurement was collected. Non-invasively recorded central waveforms (derived from the radial artery) have been validated against invasively recorded central waveforms at rest, as well as during and after cycling exercise[19]. Furthermore, good test-retest reproducibility has been demonstrated for cfPWV, central BP and AIx acquired during and after exercise[20,21].

We also evaluated the BP-independent changes in arterial stiffness by calculating an index of stiffness that is considered equivalent to the intrinsic stiffness index β_0, where β_0 is the exponent of the pressure (P)-diameter (D) relationship within the vessel[22]:

$$P = P_{\mathrm{ref}} e^{\beta_0\left(\frac{D}{D_{\mathrm{ref}}}-1\right)}.$$

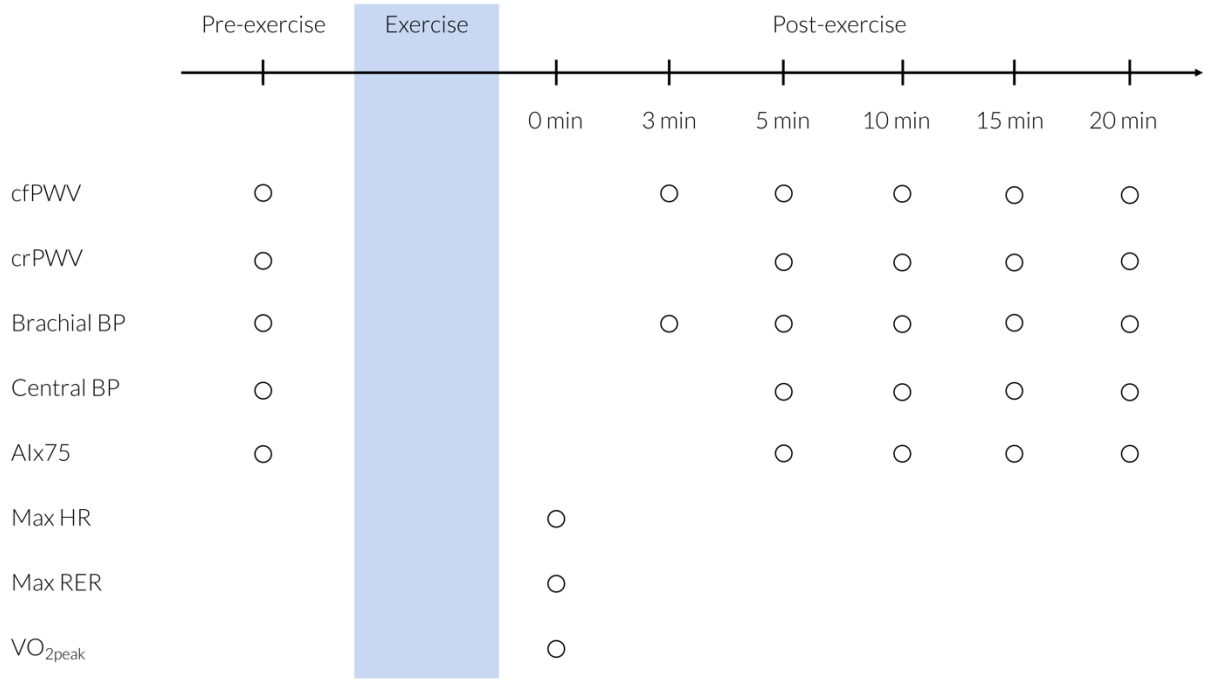
P_{ref} is a reference pressure and D_{ref} is the diameter of the artery at the reference pressure. Using cfPWV, the corresponding brachial DBP (P_{d}), and estimated blood mass density (ϱ=1.050 kg/L), and P_{ref}=100 mmHg, aortic stiffness index β_0 was determined[23] as

$$\beta_0 = \frac{\mathrm{cfPWV}^2 \cdot 2\varrho}{P_{\mathrm{d}}} - \ln\left(\frac{P_{\mathrm{d}}}{P_{\mathrm{ref}}}\right).$$

The left ventricular ejection duration was derived from the central pressure waveform and calculated as the time from the foot of the waveform to the incisura.

The timing of the measurements is summarized in Figure 1. Due to a short time window post-exercise, we prioritized the measurement of brachial BP and cfPWV at the 3-minute time point. From 5 minutes onwards, all parameters were measured, in the same order for all participants.

Figure 1. Timing of procedures included in the 'arterial stress test' protocol.



AIx75, augmentation index corrected for a HR of 75 beats/minute; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; HR, heart rate; RER, respiratory exchange ratio, VO_2, oxygen consumption.

Blood Collection

Fasting venous blood samples were obtained for the quantification of glucose and insulin levels following standard laboratory methods. In participants not taking insulin, fasting glucose and insulin values were used to compute the Homeostatic Model Assessment-Insulin Resistance (HOMA-IR).

Analysis

Demographic factors and resting parameters were compared between groups using the Student's T-test or Mann-Whitney test, as appropriate. Categorical variables were assessed using the chi-square test for independence. Linear regression models were used to evaluate between-group differences in hemodynamic parameters post-exercise. In evaluating the response to exercise, models were consistently adjusted for the baseline parameter, age, sex, as well as waist:hip ratio and angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB) use to account for group differences in these variables. ACEis/ARBs are known to influence the cardiovascular response to exercise. We further evaluated models with and without statin use due to group differences, but it should be noted that statin use was strongly correlated with T2DM status, given that clinical guidelines recommend statin therapy in patients with T2DM. Further, all measurements were adjusted for HR at the time of measurement.

To correct for the BP dependence of cfPWV, brachial DBP at the time of the measure was included as a covariate in our statistical models. DBP was chosen given that the SphygmoCor system uses the diastolic foot of the proximal and distal waveforms for the estimation of transit time, and therefore, provides a velocity measure that is dependent on DBP. However, we also assessed differences adjusting for mean arterial pressure (MAP) since we acknowledge that the brachial BP differs from central BP, and this difference may be amplified during exercise[24]. Lastly, we also evaluated two separate models, where 1) both SBP and DBP were included, and 2) SBP replaced DBP.

To evaluate the impact of T2DM on overall vascular function after physical stress, area under the curve (AUC) values were calculated for vessel hemodynamic parameters measured at baseline, 3, 5, 10, 15, and 20 minutes. In order to compare the AUC

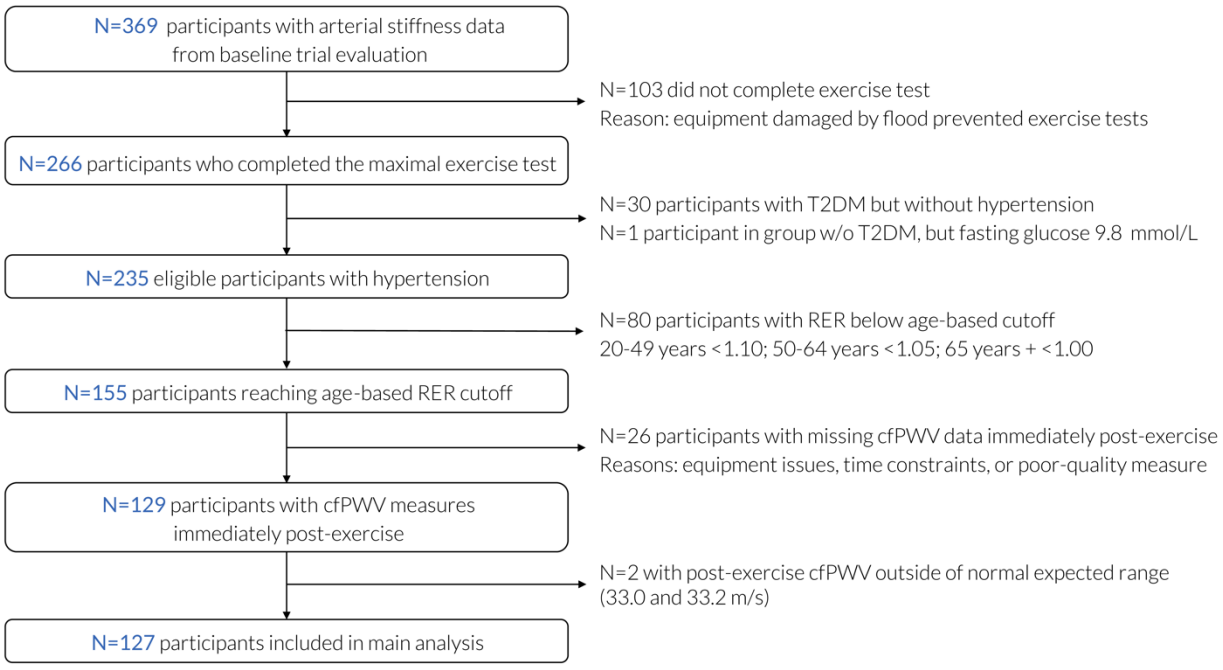
irrespective of the baseline value, a 'baseline AUC' was determined using the pre-exercise value and subtracted from the total AUC (Figure S1). Differences in the AUC were assessed using linear regression, adjusting for age, sex, waist:hip ratio, and ACEi/ARB use.

Mean differences between groups were computed with 95% confidence intervals (CIs). SAS V9.3 was used.

6.2.4 Results

Overall, 266 participants completed the exercise test. We excluded 1) participants with T2DM who did not have hypertension (n=30), 2) participants who did not meet criteria for exhaustion (n=80), and 3) participants who were missing the 3-minute post-exercise arterial stiffness measures (n=26) (Figure 2).

Figure 2. Participant flowchart outlining the number of participants excluded from the final analysis.



cfPWV, carotid-femoral pulse wave velocity; RER, respiratory exchange ratio; T2DM, type 2 diabetes mellitus.

We further identified two participants with T2DM who were significant outliers when we evaluated the post-exercise cfPWV, and whose inclusion likely exaggerated between-group differences (Table S1). Excluded participants who did not reach exhaustion during the exercise test exercised for a shorter duration, and had a lower VO_{2peak} and peak HR, but were otherwise comparable to those who were included in the final analysis (Table S2). Our main analyses compared participants with (n=66) and without T2DM (n=61).

In our main analysis, participants with T2DM had a greater waist:hip ratio, but body mass index was similar. A comparable proportion of participants with and without T2DM were treated for hypertension; however, a greater proportion with T2DM were taking ACEi/ARBs, in accordance with clinical practice guidelines (Table 1)[12]. There were differences in the lipid profile, and statins were taken by 79% of participants with T2DM versus 33% without T2DM. Fasting glucose and HOMA-IR levels were higher in those with T2DM, who had a mean hemoglobin A1c of 7.9±1.3%.

At rest, participants with T2DM had higher cfPWV and aortic stiffness β_0, and lower central and brachial DBP, but no significant differences in SBP or other hemodynamic measures were noted (Table 1).

Table 1: Baseline characteristics

Variable	**Without T2DM (n=61)**	**With T2DM (n=66)**	**P-value**
Demographic factors			
Age (years)	59.0±10.4	59.6±10.9	0.749
Women, no (%)	35 (57.4)	28 (42.4)	0.092
Body mass index (kg/m^2)	31.7±3.9	30.7±3.8	0.132
Waist circumference (cm)	101.7±9.5	103.4±10.1	0.353
Hip circumference (cm)	111.8±8.9	107.2±7.7	0.002
Waist:hip ratio	0.91±0.07	0.96±0.07	<0.001
Smoking history, no (%)			
Past Smoker	21 (34.4)	23 (35.4)	0.910
Current Smoker	2 (3.3)	5 (7.6)	0.269
Type 2 Diabetes			
Duration (years)		10.5±7.5	
Medications, no (%)			
Anti-hypertensive agents	58 (95.1)	65 (98.5)	0.273
ACEi or ARBs	39 (63.9)	62 (93.9)	<0.001
Calcium channel blockers	18 (29.5)	14 (21.2)	0.282
Diuretics	29 (47.5)	28 (42.4)	0.562
Beta-blockers	18 (29.5)	15 (22.7)	0.384
Statins	20 (32.8)	52 (78.8)	<0.001
Insulin		22 (33.3)	
Metformin		57 (86.4)	
Sulfonylureas		22 (33.3)	
Laboratory Parameters			
Fasting glucose (mmol/L)*	5.5 [5.0-6.1]	7.9 [6.5-8.8]	<0.001
Fasting insulin (pmol/L)*	65.0 [44.1-92.9]	55.8 [43.1-87.7]	0.698
Hemoglobin A1c (%)		7.6 [7.0-8.4]	
HOMA-IR	2.7 [1.7-3.6]	3.2 [2.3-4.6]	0.043
HDL (mmol/L)	1.3±0.3	1.2±0.3	0.035
LDL (mmol/L)	3.0±1.0	2.1±0.6	<0.001
Triglycerides (mmol/L)	1.3 [1.0-2.0]	1.5 [1.1-2.2]	0.326

Total cholesterol (mmol/L)	5.1±1.2	4.1±0.8	<0.001
Arterial Stiffness and Hemodynamics (measured supine)			
cfPWV (m/s)	9.2±1.9	10.3±2.7	0.009
Aortic stiffness β_0	15.1 [12.3-19.8]	19.8 [15.0-25.8]	0.003
crPWV (m/s)	8.6±1.1	8.9±1.3	0.184
Brachial SBP (mmHg)	131±13	129±15	0.630
Brachial DBP (mmHg)	82±9	78±9	0.030
Brachial PP (mmHg)	49±10	51±13	0.284
Central SBP (mmHg)	121±12	119±14	0.454
Central DBP (mmHg)	83±9	79±9	0.030
Central PP (mmHg)	38±10	40±13	0.421
MAP (mmHg)	99±10	97±10	0.120
AIx75 (%)	22.8±10.8	23.2±8.7	0.836
Pulse Pressure Amplification	1.3±0.2	1.3±0.2	0.991
Resting HR (beats/minute)	66.1±9.8	68.5±11.1	0.205
Left ventricular ejection duration (ms)	323.8±26.8	321.0±31.6	0.594
Blood Pressure (measured seated)			
Brachial SBP (mmHg)	125±12	125±16	0.983
Brachial DBP (mmHg)	79±9	76±11	0.079

Values expressed as mean±standard deviation, median [interquartile range], or number (%) as appropriate.
*Not measured in participants with T2DM on insulin therapy (n=34).

ACEi, angiotensin-converting enzyme inhibitor; Aix75, augmentation index corrected for a heart rate of 75 beats/minute; ARB, angiotensin receptor blocker; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; HR, heart rate; LDL, low density lipoprotein; MAP, mean arterial pressure; PP, pulse pressure; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus.

Response to Exercise

Unadjusted values of all parameters post-exercise are presented in the online supplement (Table S3). In adjusted analyses, no differences were observed between subjects with and without T2DM for the duration of exercise, exercise capacity (VO_{2peak}), or maximal HR (Table 2). A higher proportion of participants with T2DM had a hypertensive response to exercise compared to participants without T2DM [n=23 (35%) vs. n=11 (18%); difference 17% (95% CI 2, 32 %)]. However, the peak exercise BP (0 minutes) was not significantly different between groups in adjusted analyses. Table 2 also presents the arterial stiffness and hemodynamic parameters according to their first available measurement post-exercise (3 or 5 minutes) to demonstrate the initial response to exercise. Immediately after exercise (at 3 minutes), we observed significantly greater brachial SBP by 8.9 mmHg (95% CI 0.9, 16.9 mmHg) in participants with T2DM, but no differences in DBP or peak HR.

Interestingly, participants with T2DM had a greater increase in cfPWV and aortic stiffness β_0, as well as pulse pressure. The differences in cfPWV persisted in models adjusting for brachial DBP at the time of measurement (Table 2), MAP, and both SBP and DBP (Table S4). The increase in cfPWV was not significant when adjusting for only brachial SBP post-exercise (Table S4). In addition, it is noteworthy that the elevated SBP at 3 minutes post-exercise in T2DM was no longer significant when additionally adjusting for the corresponding post-exercise cfPWV [6.1 (95% CI -2.1, 14.2 mmHg)]. A significant between-group difference in aortic stiffness β_0 remained when SBP was included (7.70, 95% CI 0.05, 15.34). Univariate, partially adjusted, and fully adjusted models for aortic stiffness β_0 are presented in Table S5.

No significant differences in central BP, crPWV, AIx75, or left ventricular ejection duration were observed. Calibration of central BP with brachial MAP and DBP instead of SBP and DBP did not change the results (Table S6).

Table 2. Between-group differences in arterial stiffness and hemodynamics in initial response to exercise each parameter (3 or 5 minutes)

Variable	Without T2DM (n=61)	With T2DM (n=66)	Mean difference (with-without T2DM) (95% CI)
Immediately Post-Exercise			
Exercise time (minutes)	14.8 (14.3, 15.3)	15.0 (14.5, 15.5)	0.2 (-0.6, 1.0)
VO_{2peak} (mL/kg/min)	24.3 (23.1, 25.5)	24.0 (22.9, 25.2)	-0.3 (-2.0, 1.5)
Max HR (beats/min)	154.0 (148.8, 159.2)	153.1 (148.2, 158.0)	-0.9 (-8.5, 6.7)
Peak SBP (mmHg)	173.1 (166.2, 180.0)	182.8 (176.3, 189.4)	9.7 (-0.4, 19.8)
Peak DBP (mmHg)	78.0 (74.1, 81.9)	74.6 (70.8, 78.4)	-3.4 (-9.2, 2.4)
3 minutes			
Brachial SBP (mmHg)	164.0 (158.6, 169.5)	173.0 (167.8, 178.2)	8.9 (0.9, 16.9)
Brachial DBP (mmHg)	82.7 (80.7, 84.8)	84.1 (82.1, 86.1)	1.4 (-1.7, 4.5)
Brachial PP (mmHg)	81.4 (76.886.1)	88.8 (84.4, 93.2)	7.4 (0.6, 14.2)
cfPWV (m/s)	12.8 (12.0, 13.7)	14.5 (13.7, 15.3)	1.6 (0.4, 2.9)
Aortic stiffness β_0	35.0 (29.7, 40.2)	43.6 (38.7, 48.6)	8.7 (1.0, 16.4)
HR (beats/min)	98.3 (94.7, 101.8)	98.6 (95.3, 102.0)	0.4 (-4.8, 5.6)
5 minutes			
crPWV (m/s)	8.7 (8.3, 9.0)	8.9 (8.6, 9.2)	-0.3 (-0.2, 0.7)
Central SBP (mmHg)	118.2 (115.0, 121.4)	121.1 (118.0, 124.2)	2.9 (-1.7, 7.7)
Central DBP (mmHg)	79.6 (77.6, 81.6)	81.2 (79.3, 83.1)	1.6 (-1.4, 4.6)

Central PP (mmHg)	38.6 (36.2, 41.0)	40.0 (37.7, 42.2)	1.36 (-2.1, 5.0)
AIx75 (%)	26.0 (24.3, 27.7)	24.4 (22.8, 26.0)	-1.6 (-4.1, 1.0)
Ejection duration (ms)	302.6 (296.1, 309.1)	304.8 (298.6, 311.0)	2.2 (-7.3, 11.7)

AIx75, augmentation index corrected for a heart rate of 75 beats/minute; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; VO_{2peak}; peak oxygen consumption.

Adjusted means (95% CI) are presented.
Exercise time, VO_{2peak}, maximal HR, ejection duration, HR and AIx75 are adjusted for age, sex, waist:hip ratio and ACEi/ARB use.
cfPWV and crPWV are adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, as well as HR and MAP at the time of measurement.
Aortic stiffness β_0 and BP is adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, and HR at the time of measurement.

Participants with T2DM exhibited a greater AUC for cfPWV, aortic stiffness β_0, and brachial SBP and DBP than participants without T2DM (Table 3).

Table 3: Between-group differences in the area under the curve for arterial stiffness and hemodynamics in response to exercise

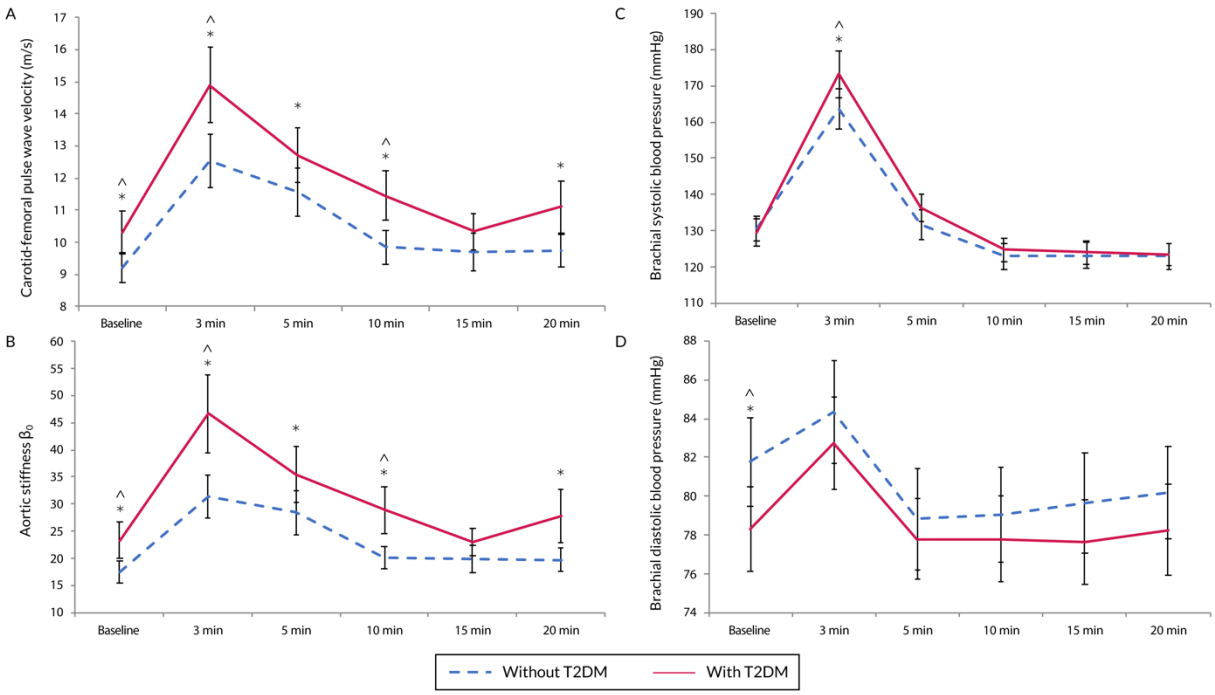
Area Under the Curve Variable	Without T2DM (n=61)	With T2DM (n=66)	Mean difference (with-without T2DM) (95% CI)
Brachial SBP (mmHg·min)	-6.6 (-64.6, 51.4)	79.9 (25.5, 134.3)	86.5 (2.2, 170.7)
Brachial DBP (mmHg·min)	-42.7 (-73.7, -11.7)	9.4 (-19.7, 38,4)	52.1 (7.1, 97.1)
Brachial PP (mmHg·min)	36.2 (-8.4, 80.7)	70.5 (28.7, 112.4)	34.4 (-30.4, 99.2)
cfPWV (m/s·min)	20.7 (12.9, 28.6)	36.3 (28.6, 44.0)	15.5 (4.0, 27.1)
Aortic stiffness β_0	105.3 (66.1, 144.5)	175.6 (137.5, 213.6)	70.2 (12.6, 127.8)
crPWV (m/s·min)	-2.3 (-7.7, 3.1)	-0.7 (-6.0, 4.7)	1.6 (-6.4, 9.7)
Central SBP (mmHg·min)	-134.1 (-184.4, -83.9)	-79.1 (-126.3, -31.8)	55.1 (-18.4, 128.6)
Central DBP (mmHg·min)	-33.3 (-64.5, -2.2)	0.7 (-28.6, 30.0)	34.0 (-11.6, 79.6)
MAP (mmHg·min)	-63.3 (-97.6, -28.9)	-26.4 (-58.6, 5.9)	36.9 (-13.3, 87.1)
Central PP (mmHg·min)	-100.8 (-135.7, -65.9)	-79.8 (-112.5, -47.0)	21.0 (-30.0, 72.1)
AIx75 (%·min)	-9.0 (-31.3, 13.3)	-33.7 (-55.0, -12.3)	-24.7 (-57.5, 8.2)

All analyses were adjusted for age, sex, waist:hip ratio, and ACEi/ARB use. Adjusted means (95% CI) are presented.

AIx75, augmentation index corrected for a heart rate of 75 beats/minute; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; T2DM, type 2 diabetes mellitus.

There were no differences between subjects with and without T2DM beyond 3 minutes for brachial SBP (Figure 3). While the overall AUC was different between groups for brachial DBP, there were no differences at 3 minutes, or at other points during the recovery. cfPWV and aortic stiffness β_0 were both significantly different at 3, 5, 10 and 20 minutes in unadjusted analyses, and only at 3 and 10 minutes in adjusted analyses, accounting for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, and DBP (cfPWV only) and HR at the time of measurement. Between-group differences for all parameters during recovery (5, 10, 15 and 20 minutes) are presented in Table S7.

Figure 3. Trajectory of unadjusted of arterial stiffness and blood pressure in response to exercise.



cfPWV, carotid-femoral pulse wave velocity; T2DM, type 2 diabetes mellitus.
A) cfPWV, B) aortic stiffness β_0, C) systolic blood pressure and D) diastolic blood pressure changes from rest to post-exercise at 3, 5, 10, 15, and 20 minutes. Error bars represent 95% confidence intervals. Linear regression models were used. *Indicates a significant between-group difference in unadjusted analyses, and ^ indicates a significant difference in adjusted analyses (described in Table 2).

6.2.5 Discussion

By incorporating exercise as a vascular stressor, we provide evidence of a greater increase in cfPWV and aortic stiffness β_0 in individuals with T2DM, independently of resting arterial stiffness, and the brachial BP post-exercise. In a fully adjusted model, we observed a difference in cfPWV of 1.6 m/s between individuals with and without T2DM. A meta-analysis of 17 longitudinal studies (n=15,877 individuals) showed that a 1 m/s increase in resting aortic stiffness corresponds to a 14%, 15%, and 15% increased risk of CVD events, CVD mortality and all-cause mortality, respectively, adjusting for traditional CVD risk factors[7]. This robust association was confirmed in a more recent large individual participant meta-analysis in 17,635 individuals[8]. While the clinical significance of differences in cfPWV post-exercise has not been established, the magnitude of the difference in cfPWV observed in our study is not trivial.

Calculating the AUC allowed us to generate a single variable that summarizes multiple longitudinal measurements, capturing the combined response and recovery of each parameter to maximal stress. Our results, indicating significant differences in the AUC for cfPWV and aortic stiffness β_0, support an overall difference in the response of arterial stiffness to exercise between individuals with and without T2DM. The AUC for brachial SBP was also higher in individuals with T2DM but this was mainly driven by differences between groups immediately post-exercise, given that both groups followed a similar trajectory afterwards, i.e., from 5 to 20 minutes post-exercise.

In subjects with T2DM, we observed a greater increase in brachial SBP at 3 minutes post-exercise, which is in line with findings by Scott and colleagues demonstrating an excessive rise in brachial SBP in response to maximal treadmill exercise in adults with T2DM compared to healthy controls[3]. While they also observed a significantly greater

increase in central SBP immediately post-exercise (<3 minutes), we only observed a trend for an increase, likely because central BP in our study was captured 5 minutes post-exercise, at which point values had returned to baseline.

To our knowledge, no prior studies have evaluated the arterial stiffness response immediately post-maximal exercise in adults with T2DM. A study of a hypertensive population demonstrated elevated cfPWV 40 minutes and 1 hour after maximal cycling exercise compared with baseline levels[25]. This increase post-exercise was not observed in normotensive controls; however, this analysis did not compare the post-exercise cfPWV between groups. Instead, we have demonstrated an elevated cfPWV response in individuals with T2DM and hypertension compared to subjects with hypertension alone. Climie and colleagues compared the arterial stiffness and hemodynamic response to a short bout of light-moderate cycling exercise between individuals with T2DM and healthy controls[26]. They measured cfPWV while still on the cycle ergometer, enabling more immediate cfPWV measurements. They observed a significantly higher cfPWV post-exercise in individuals with T2DM (unadjusted); however, this analysis did not account for differences in resting cfPWV or other covariates, as this was not the main interest of this paper.

The relationship between arterial stiffness and BP is bi-directional and complex[27]. Arterial stiffening increases the amplitude of the forward traveling pressure waves, as well as the speed of propagation of both the forward and backward waves[6]. Consequently, the reflected waves return earlier during the cardiac cycle and become superimposed on the systolic part of the forward wave, leading to elevated central SBP and a widened pulse pressure[6]. Interestingly, during light-moderate cycling exercise, the elevation in central SBP is mainly due to an increase in the amplitude of the forward travelling wave, rather than reflected waves[28]. Therefore, arterial stiffness and forward

wave amplitude both contribute to the BP change observed during exercise. Conversely, given the exponential relationship between artery diameter and pressure, there is a clear acute relationship between the arterial BP and stiffness, represented by the tangent slope[23]. Therefore, the intrinsic stiffness of the artery will depend on BP. This bi-directional relationship complicates the assessment of arterial stiffness independently of BP; however, different mechanisms for evaluating the BP-independent response of arterial stiffness have been proposed[23]. Most commonly, arterial stiffness is statistically adjusted for BP at the time of measurement. Adjusting for the MAP is often recommended[6]; however, adjusting for the DBP may be more relevant as this represents the pressure in the artery when the transit time is calculated[29]. We have performed analyses adjusting for brachial DBP as well as for MAP. Hermeling and colleagues have demonstrated that PWV changes dramatically over the cardiac cycle, reporting a mean difference of 2.4 m/s between the diastolic and systolic phase (range 0.8-4.4 m/s)[30]. In our study we have calculated transit time using the foot of the arterial pressure waveform, and therefore, elected to adjust analyses for the brachial DBP. Similarly, aortic stiffness β_0 is derived by inputting the DBP. Spronck and colleagues demonstrated that cardio-ankle vascular index (CAVI), which has been proposed to be a pressure-independent estimate of the intrinsic stiffness β, may show a residual acute BP dependence[23]. They provide a modified formula that theoretically removes the acute BP dependence, yielding $CAVI_0$. Our inclusion of cfPWV versus heart-to-ankle PWV in the case of $CAVI_0$ provides an estimate of the intrinsic stiffness β_0 in the central elastic arteries. In our study, statistical correction of cfPWV for DBP, and the aortic stiffness β_0 yielded comparable results. Similar to cfPWV, a significant aortic stiffness β_0 difference remained when adjusting for SBP. This observation strengthens our finding that the observed difference in arterial stiffness between groups is independent of the intrinsic arterial stiffness dependence on

DBP (as corrected for through calculation of aortic stiffness β_0), as well as independently of SBP. We also observed an elevated cfPWV response in models adjusting for MAP. A significant association between brachial SBP immediately post-exercise and the corresponding post-exercise cfPWV was also noted. Specifically, the elevated SBP response post-exercise in T2DM was no longer significant when adjusting for the corresponding post-exercise cfPWV. On the other hand, the higher cfPWV response in T2DM was independent of brachial SBP and DBP post-exercise. Taken together, these findings indicate that arterial stiffness may mediate the exaggerated SBP increase.

Participants with T2DM had elevated arterial stiffness at rest, which is likely a function of structural changes of the arteries. High levels of circulating glucose lead to the development of advanced glycation end products, whereby glucose forms cross-links with collagen proteins within the arteries, and therefore, may alter the important balance between elastin and collagen[1]. Hyperglycemia causes the activation of protein kinase C, which leads to the generation of reactive oxygen species, and inflammation, further altering the structural and functional integrity of vascular wall[1]. When assessing post-exercise values of cfPWV, we have adjusted for resting values of cfPWV. Furthermore, we have demonstrated that the increase in arterial stiffness after acute exercise occurs independently of BP at the time of measurement, suggesting that these changes are due to changes in intrinsic properties of the arterial wall. As structural changes in such time frame (minutes) are unlikely, we attribute differences in response to exercise mainly to functional changes. For example, individuals with T2DM have endothelial dysfunction; higher levels of endothelin-1 and reduced nitric oxide bioavailability may cause an impaired vasodilatory response and increased arterial stiffness post-exercise[1]. Additionally, excess sympathetic activity in individuals with T2DM may potentiate greater exercise-induced vasoconstriction[1]. It is noteworthy that vasoconstriction does

not always lead to a functional increase in stiffness; for example, in healthy subjects, vasoconstriction may shift pressure load bearing towards elastin, offloading the stiff collagen. However, in individuals with T2DM who have impaired arterial function, vasoconstriction presumably leads to increased functional stiffness[31].

The sample size of our study is relatively small; however, we demonstrated conclusive between-group differences in our main outcome, while adjusting for relevant covariates. This study constituted a secondary analysis of our SMARTER trial[10], and thus we did not carry out power calculations *a priori*. Due to time constraints post-exercise, we could only obtain single measurements at each time point and were only able to measure select indices of arterial stiffness (i.e., cfPWV) at the 3-minute time point. Thus, we were not able to capture differences in central hemodynamic parameters earlier, as these measurements were only obtained after 5 minutes post-exercise. To this end, because we did not have central DBP measures immediately after exercise we have included brachial DBP in our models. However, DBP is relatively stable, with little difference between peripheral and central values[6]. Pulse pressure amplification increases during exercise in healthy individuals[24]; however, a follow-up study by the same group demonstrated that the degree of amplification is reduced in older patients with hypercholesterolemia[32]. Moreover, the pulse pressure amplification is likely driven more by an increase in SBP. We examined central and peripheral BP at 5 minutes; although on average brachial SBP was 15 mmHg greater than central SBP, there was only a 2 mmHg average difference for DBP (data not shown). Therefore, while brachial DBP seems to closely estimate the central DBP, we still included analyses adjusting for MAP (mainly driven by DBP)[17]. Following guidelines, measurements of arterial stiffness and hemodynamics were performed in a supine position pre- and post-exercise; however, we were not able to control for the possible postural influence of lying down after treadmill exercise on vessel

hemodynamics. Since we aimed to provoke maximal changes in arterial stiffness and hemodynamics, a graded treadmill test was selected over supine cycling exercise. Lastly, since all participants included in our analysis were hypertensive, the results of this study may not be generalizable to younger, lower-risk individuals with T2DM.

Perspectives

Our study has demonstrated that evaluating the exercise-induced response of arterial stiffness provides additional information by capturing the effect of T2DM on the ability of the arteries to respond to increased demands during exercise. Central arterial stiffness directly influences BP and likely contributes to the exaggerated BP response in participants with T2DM. Increased central arterial stiffness has a number of clinical consequences; it imposes a greater load on the left ventricle, decreases coronary perfusion, and exposes the microcirculation and end-organs to increased pulsatile pressure. Given that we do not spend our lives at rest, and physical stress commonly occurs during daily activities, this altered arterial stiffness response to strenuous exercise may contribute to the increased risk for CVD events in these individuals. The 'arterial stress test' may serve as a useful model for evaluating vascular impairment and CVD risk in individuals with T2DM. Future studies are needed to confirm the clinical utility of this model.

6.2.6 Acknowledgements

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6.2.7 Conflicts of Interest

None.

6.2.8 References

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6.3 Supplementary Material – Manuscript 4

Table S1. Between-group differences in arterial stiffness and hemodynamics in response to exercise included two cfPWV outliers removed from main analysis

Variable	**Without T2DM (n=61) Mean (95% CI)**	**With T2DM (n=68) Mean (95% CI)**	**Mean difference (with-without T2DM) (95% CI)**
Arterial Stiffness and Hemodynamic Measures at 3 minutes			
Brachial Systolic BP (mmHg)	164.5 (159.1, 169.9)	173.1 (168.1, 178.2)	**8.7 (0.9, 16.5)**
Brachial Diastolic BP (mmHg)	82.7 (80.6, 84.8)	84.3 (82.4, 86.2)	1.6 (-1.4, 4.6)
Brachial PP (mmHg)	81.9 (77.2, 86.5)	88.8 (84.5, 93.1)	**6.9 (0.3, 13.6)**
cfPWV (m/s)	13.0 (12.0, 14.0)	15.1 (14.2, 16.0)	**2.1 (0.7, 3.6)**
Aortic stiffness β_0	34.4 (27.5, 41.4)	48.3 (41.9, 54.8)	**13.9 (3.8, 24.0)**
HR (beats/min)	98.3 (94.7, 101.8)	98.9 (95.6, 102.2)	0.6 (-4.5, 5.7)
Arterial Stiffness and Hemodynamic Measures at 5 minutes			
crPWV (m/s)	8.7 (8.3, 9.0)	8.9 (8.6, 9.2)	0.2 (-0.3, 0.7)
Central Systolic BP (mmHg)	118.3 (115.1, 121.5)	121.1 (118.1, 124.1)	2.9 (-1.7, 7.5)
Central Diastolic BP (mmHg)	79.6 (77.6, 81.6)	81.3 (79.4, 83.2)	1.7 (-1.2, 4.6)
Central PP (mmHg)	38.6 (36.3, 41.0)	39.9 (37.6, 42.1)	1.2 (-2.2, 4.6)
AIx75 (%)	25.9 (24.3, 27.6)	24.4 (22.8, 26.0)	-1.6 (-4.0, 0.8)

AIx75, augmentation index corrected for a heart rate of 75 beats/minute; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; PP, pulse pressure.
Bolded values indicate a significant absolute difference between groups.
cfPWV, crPWV, and Augmentation Index are adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, HR, and MAP.
Aortic stiffness β_0 is adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, and HR.
Blood pressure is adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, and HR.
HR and AIx75 at 3 minutes are adjusted for the pre-exercise value, age, sex, waist:hip ratio, and ACEi/ARB use.

Table S2. Characteristics of participants excluded from analyses based on failure to meet criteria for exhaustion during maximal exercise

Variable	Included in Analysis (n=127)	Did not meet criteria for exhaustion (n=80)	P-value
Age, years	59.3 ± 10.6	59.8 ± 11.4	0.767
Women, no (%)	63 (49.6%)	49 (61.3%)	0.102
Body mass index, kg/m^2	31.2 ± 3.9	31.9 ± 4.2	0.207
Waist circumference, cm	102.6 ± 9.8	104.2 ± 11.5	0.228
Hip circumference, cm	109.4 ± 8.6	111.9 ± 9.6	0.053
Waist to hip circumference	0.94 ± 0.07	0.93 ± 0.08	0.584
Duration, years	10.5 ± 7.5	10.2 ± 8.0	0.829
Arterial Stiffness and Hemodynamics			
cfPWV (m/s)	9.8 ± 2.4	9.7 ± 1.9	0.851
Brachial Systolic BP (mmHg)	130 ± 14	129 ± 15	0.542
Brachial Diastolic BP (mmHg)	80 ± 9	81 ± 9	0.735
Brachial PP (mmHg)	50 ± 12	49 ± 12	0.632
Resting HR (beats/minute)	67.4 ± 10.6	67.9 ± 12.9	0.737
Exercise Parameters			
Exercise time (minutes)	14.9 ± 2.4	13.0 ± 3.3	**<0.001**
VO_{2peak} (mL/kg/min)	24.3 ± 6.2	19.3 ± 5.6	**<0.001**
Peak HR (beats/minute)	153.7 ± 23.9	138.6 ± 23.7	**<0.001**

Values expressed as mean ± standard deviation or number (%) as appropriate.

BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; HDL, high density lipoprotein; HOMA-IR, homeostatic model assessment-insulin resistance; HR, heart rate; MAP, mean arterial pressure; PP, pulse pressure; VO_{2peak}, peak oxygen consumption.

Table S3. Unadjusted values of post-exercise arterial stiffness, hemodynamics, and exercise parameters

Variable	Without T2DM (n=61) Mean±SD	With T2DM (n=66) Mean±SD	Mean difference (with-without T2DM) (95% CI)
Exercise time (minutes)	14.8±5.3	15.1±2.4	0.2 (-0.6, 1.1)
VO_{2peak} (mL/kg/min)	24.3±6.5	24.2±6.0	-0.1 (-2.3, 2.1)
Max HR (beats/min)	154±22	153±25	-1 (-9, 8)
Peak SBP (mmHg)	171±27	185±30	**14 (4, 25)**
Peak DBP (mmHg)	80±17	73±13	-7 (-12, -2)
Brachial SBP (mmHg)	164±22	173±26	**10 (1, 18)**
Brachial DBP (mmHg)	84 ±11	83±10	-2 (-5, 2)
Brachial PP (mmHg)	79±18	90±22	**11 (4, 18)**
cfPWV (m/s)	12.5±3.3	14.9±4.7	**2.4 (0.9, 3.8)**
Aortic stiffness β_0	32±16	47±29	**15.2 (6.9, 23.6)**
HR (beats/min)	98±17	99±17	1 (-5, 7)
crPWV (m/s)	8.6±1.3	8.9±1.5	0.4 (-0.1, 0.9)
Central SBP (mmHg)	119±16	121±14	2 (-4, 8)
Central DBP (mmHg)	81±10	80±9	-1 (-5, 2)
Central PP (mmHg)	37±11	41±14	3 (-1, 8)
AIx75 (%)	27.3±8.8	24.0±9.4	-2.3 (-5.7, 1.0)
Ejection duration (ms)	303.9±24.6	303.1±29.5	-0.8 (-10.7, 9.1)

AIx75, augmentation index corrected for a heart rate of 75 beats/minute; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure; VO_{2peak}; peak oxygen consumption.

Table S4. Mean difference in cfPWV at 3 minutes post-exercise between adults with and without T2DM in univariate, partially adjusted, and fully adjusted models

Model	Included Variables	Mean Difference (with-without T2DM) (95% CI)
1	Unadjusted	**2.37 (0.93, 3.81)**
2	Pre-exercise value	**1.21 (0.02, 2.40)**
3	Model 2 and age, sex	**1.32 (0.11, 2.52)**
4	Model 3 and WHR, ACEi/ARB use	**1.38 (0.05, 2.71)**
5	Model 4 and HR at 3 minutes	**1.40 (0.11, 2.69)**
6a	Model 5 and diastolic BP at 3 minutes	**1.59 (0.34, 2.85)**
6b	Model 5 and MAP at 3 minutes	**1.36 (0.13, 2.59)**
6c	Model 5 and systolic BP at 3 minutes	1.17 (-0.08, 2.43)
6d	Model 5 and systolic and diastolic BP at 3 minutes	**1.36 (0.09, 2.63)**
7a	Model 6a and statin use	**1.35 (0.01, 2.70)**
7b	Model 6b and statin use	1.14 (-0.18, 2.47)
7c	Model 6c and statin use	1.01 (-0.34, 2.36)
7d	Model 6d and statin use	1.15 (-0.20, 2.51)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; HR, heart rate; MAP, mean arterial pressure; T2DM, type 2 diabetes mellitus.

Table S5. Mean difference in aortic stiffness β0 at 3 minutes post-exercise between adults with and without T2DM in univariate, partially adjusted, and fully adjusted models

Model	Included Variables	Mean Difference (with-without T2DM) (95% CI)
1	Unadjusted	**15.2 (6.92, 23.55)**
2	Pre-exercise value	**7.93 (0.95, 14.92)**
3	Model 2 and age, sex	**9.05 (1.96, 16.15)**
4	Model 3 and WHR, ACEi/ARB use	**8.61 (0.81, 16.42)**
5	Model 4 and HR at 3 minutes	**8.67 (0.96, 16.37)**
6	Model 5 and SBP at 3 minutes	**7.70 (0.05, 15.34)**
7	Model 5 and statin use	7.22 (-1.02, 15.46)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; HR, heart rate; MAP, mean arterial pressure; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure.

Table S6. Central Blood Pressure Parameters Calibrated with Brachial Mean Arterial Pressure and Diastolic Blood Pressure

Variable	Without T2DM (n=61) Mean (95% CI)	With T2DM (n=66) Mean (95% CI)	Mean difference (with-without T2DM) (95% CI)
Resting			
Central SBP (mmHg)	117.9 (115.0, 120.9)	117.0 (113.7, 120.3)	-1.0 (-5.4, 3.4)
Central DBP (mmHg)	82.8 (80.6, 85.1)	79.3 (77.0, 81.5)	-3.5 (-6.7, -0.4)
Central PP (mmHg)	35.1 (32.8, 37.5)	37.7 (34.8, 40.7)	2.6 (-1.2, 6.3)
5min post-exercise			
Central SBP (mmHg)	115.1 (112.0, 118.1)	119.5 (116.6, 122.5)	4.4 (-0.02, 8.9)
Central DBP (mmHg)	79.5 (77.5, 81.5)	81.0 (79.1, 82.9)	1.5 (-1.5, 4.5)
Central PP (mmHg)	28.9 (27.0, 30.9)	30.5 (28.6, 32.3)	1.5 (-1.3, 4.4)

DBP, diastolic blood pressure; PP, pulse pressure; SBP, systolic blood pressure.

Pre-exercise measures are unadjusted. Post-exercise central SBP and DBP is adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, and HR at the time of measurement. Adjusted means are presented.

Table S7. Between-group differences in arterial stiffness and hemodynamics at 5, 10, 15, and 20 minutes post-exercise

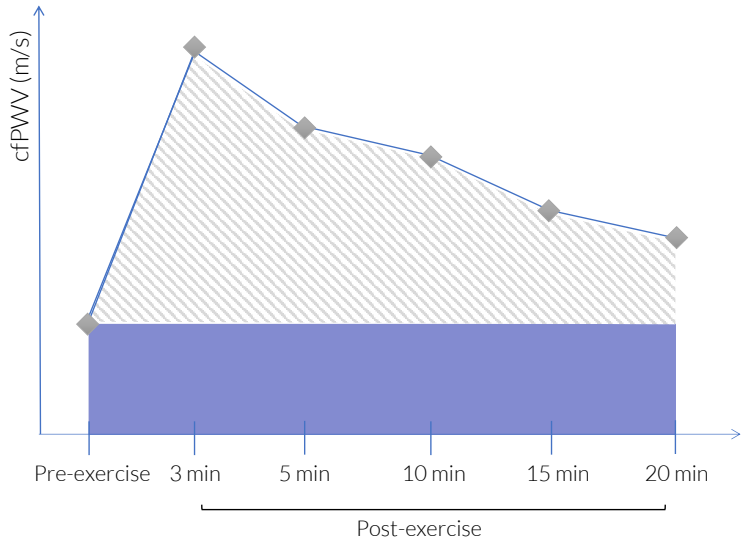
Variable	Without T2DM (n=61) Mean (95% CI)	With T2DM (n=66) Mean (95% CI)	Mean difference (with-without T2DM) (95% CI)
Arterial Stiffness and Hemodynamic Measures at 5 minutes			
Brachial SBP (mmHg)	131.8 (128.4, 135.2)	136.5 (133.3, 139.7)	4.7 (-0.2, 9.7)
Brachial DBP (mmHg)	77.2 (75.3, 79.1)	79.3 (77.5, 81.1)	2.1 (-0.8, 4.9)
Brachial PP (mmHg)	54.6 (51.7, 57.4)	57.2 (54.5, 59.9)	2.6 (-1.5, 6.8)
Central SBP (mmHg)	118.2 (115.0, 121.4)	121.1 (118.0, 124.2)	2.9 (-1.7, 7.7)
Central DBP (mmHg)	79.6 (77.6, 81.6)	81.2 (79.3, 83.1)	1.6 (-1.4, 4.6)
Central PP (mmHg)	38.6 (36.2, 41.0)	40.0 (37.7, 42.2)	1.36 (-2.1, 5.0)
cfPWV (m/s)	11.9 (11.3, 12.5)	12.4 (11.8, 13.1)	0.5 (-0.4, 1.5)
crPWV (m/s)	8.7 (8.3, 9.0)	8.9 (8.5, 9.2)	0.2 (-0.3, 0.7)
Aortic stiffness β_0	31.7 (27.9, 35.5)	32.6 (29.0, 36.3)	0.9 (-4.7, 6.6)
HR (beats/min)	89.5 (87.0, 92.1)	88.8 (86.4, 91.2)	-0.7 (-4.4, 3.0)
AIx75 (%)	26.0 (24.3, 27.7)	24.4 (22.8, 26.8)	-1.6 (-4.1, 0.91)
Arterial Stiffness and Hemodynamic Measures at 10 minutes			
Brachial SBP (mmHg)	122.5 (119.7, 125.3)	125.6 (122.9, 128.2)	3.1 (-1.0, 7.2)
Brachial DBP (mmHg)	77.2 (75.5, 79.0)	79.5 (77.8, 81.1)	2.2 (-0.4, 4.9)
Brachial PP (mmHg)	44.9 (42.5, 47.2)	46.4 (44.2, 48.6)	1.5 (-1.9, 5.0)
Central SBP (mmHg)	110.8 (108.1, 113.5)	113.1 (110.6, 115.7)	2.3 (-1.6, 6.3)
Central DBP (mmHg)	78.9 (77.0, 80.8)	80.5 (78.8, 82.2)	1.6 (-1.1, 4.3)
Central PP (mmHg)	31.5 (29.6, 33.4)	32.9 (31.2, 34.7)	1.4 (-1.3, 4.2)
cfPWV (m/s)	10.1 (9.5, 10.6)	11.3 (10.8, 11.8)	**1.3 (0.4, 2.1)**
crPWV (m/s)	8.4 (8.1, 8.7)	8.7 (8.4, 8.9)	0.3 (-0.2, 0.7)
Aortic stiffness β_0	22.0 (19.0, 24.9)	27.4 (24.7, 30.2)	**5.5 (1.1, 9.8)**
HR (beats/min)	87.0 (84.7, 89.4)	86.1 (83.9, 88.4)	-0.9 (-4.4, 2.5)
AIx75 (%)	22.5 (21.0, 23.9)	22.6 (21.2, 24.0)	0.1 (-2.0, 2.3)
Arterial Stiffness and Hemodynamic Measures at 15 minutes			
Brachial SBP (mmHg)	122.6 (119.8, 125.5)	124.8 (122.1, 127.5)	2.2 (-2.0, 6.3)
Brachial DBP (mmHg)	77.8 (76.1, 79.5)	79.4 (77.7, 81.0)	1.5 (-1.0, 4.1)
Brachial PP (mmHg)	44.4 (42.0, 46.9)	45.8 (43.5, 48.2)	1.4 (-2.3, 5.0)

Central SBP (mmHg)	110.1 (107.7, 112.6)	112.1 (109.7, 114.5)	1.9 (-1.7, 5.6)
Central DBP (mmHg)	79.5 (77.7, 81.2)	80.5 (78.8, 82.2)	1.0 (-1.6, 3.6)
Central PP (mmHg)	30.3 (28.4, 32.2)	32.0 (30.1, 33.9)	1.7 (-1.2, 4.5)
cfPWV (m/s)	9.8 (9.3, 10.4)	10.3 (9.8, 10.8)	0.4 (-0.3, 1.2)
crPWV (m/s)	8.7 (8.4, 9.0)	8.7 (8.4, 9.0)	0.1 (-0.4, 0.5)
Aortic stiffness β_0	20.9 (18.6, 23.2)	22.3 (20.1, 24.5)	1.4 (-2.1, 4.8)
HR (beats/min)	85.6 (83.3, 87.9)	84.2 (82.0, 86.4)	-1.3 (-4.7, 2.0)
AIx75 (%)	20.5 (19.1, 21.8)	21.1 (19.7, 22.5)	0.6 (-1.4, 2.7)
Arterial Stiffness and Hemodynamic Measures at 20 minutes			
Brachial SBP (mmHg)	122.6 (119.8, 125.5)	124.1 (121.4, 126.8)	1.5 (-2.6, 5.6)
Brachial DBP (mmHg)	78.5 (76.7, 80.2)	80.0 (78.3, 81.6)	1.5 (-1.1, 4.0)
Brachial PP (mmHg)	43.8 (41.2, 46.4)	44.5 (42.0, 46.9)	0.7 (-3.1, 4.5)
Central SBP (mmHg)	109.9 (107.3, 112.5)	111.2 (108.8, 113.6)	1.3 (-2.4, 5.1)
Central DBP (mmHg)	80.4 (78.6, 82.2)	80.9 (79.2, 82.5)	0.5 (-2.1, 3.1)
Central PP (mmHg)	29.2 (27.2, 31.2)	30.6 (28.7, 32.4)	1.3 (-1.6, 4.2)
cfPWV (m/s)	10.1 (9.7, 10.6)	10.8 (10.4, 11.3)	0.7 (-0.02, 1.4)
crPWV (m/s)	8.5 (8.1, 8.9)	8.7 (8.3, 9.1)	0.2 (-0.4, 0.8)
Aortic stiffness β_0	23.0 (20.5, 25.4)	25.0 (22.7, 27.4)	2.1 (-1.5, 5.7)
HR (beats/min)	84.3 (82.1, 86.6)	83.7 (81.6, 85.8)	-0.6 (-3.9, 2.6)
AIx75 (%)	19.4 (17.9, 20.9)	19.1 (17.7, 20.5)	-0.3 (-2.5, 1.9)

AIx75, augmentation index corrected for a heart rate of 75 beats/minute; BP, blood pressure; cfPWV, carotid-femoral pulse wave velocity; crPWV, carotid-radial pulse wave velocity; PP, pulse pressure.

Bolded values indicate a significant absolute difference between groups.
cfPWV, crPWV, and Augmentation Index are adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, HR, and MAP.
Aortic stiffness β0 is adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, and HR.
Blood pressure is adjusted for the pre-exercise value, age, sex, waist:hip ratio, ACEi/ARB use, and HR.
HR and AIx75 at 3 minutes are adjusted for the pre-exercise value, age, sex, waist:hip ratio, and ACEi/ARB use.

Figure S1. Area under the curve formula



cfPWV AUC = Total AUC – Baseline AUC

cfPWV AUC=pre_cfPWV*2+((3min_cfPWV-pre_cfPWV)*2)/2+3min_cfPWV*3+((5min_cfPWV-3min_cfPWV)*3)/2+5min_cfPWV*5+((10min_cfPWV-5min_cfPWV)*5)/2+10min_cfPWV*5+((15min_cfPWV-10min_cfPWV)*5)/2+15min_cfPWV*5+((20min_cfPWV-15min_cfPWV)*5/2)-pre_cfPWV*20;

CHAPTER 7:

Methodological Considerations for the Measurement of Physical Activity and Arterial Stiffness

This chapter encompasses two methodological studies relevant to my thesis work.

7.1 Preamble – Manuscript 5

Accelerometers are increasingly used as a more accurate means to quantify physical levels in free-living settings; they eliminate the recall bias associated with self-reported physical activity assessment and generate outputs on the various components of physical activity (volume, intensity, duration). In the SMARTER trial, a subset of participants also wore GTX+ accelerometers for a 1-week period before and after the intervention. The trial was developed when researchers were first starting to consider using the wrist location over the validated hip location. Wearing an accelerometer at the wrist was more convenient for participants and led to higher compliance. Therefore, the wrist location was originally selected for the free-living assessment of step counts and physical activity levels in the first 46 participants enrolled in the SMARTER trial. However, concerns about the agreement with pedometer-derived step counts led us to switch to the waist site for the subsequent 280 participants. The switch provided me with the opportunity to compare accelerometer-derived step counts from waist and wrist locations in participants who simultaneously wore a pedometer at the waist for a 1-week period. Importantly, I evaluated the impact of accelerometer placement in the context of cfPWV, a clinical outcome that was associated with step counts in this cohort[180]. This manuscript was published in April 2018 by the *Journal of Science and Medicine in Sport*.

7.2 Content – Manuscript 5

The Impact of Accelerometer Wear Location on the Relationship between Step Counts and Arterial Stiffness in Adults Treated for Hypertension and Diabetes

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7.2.1 Abstract

Objectives: Accelerometer placement at the wrist is convenient and increasingly adopted despite less accurate physical activity (PA) measurement than with waist placement. Capitalizing on a study that started with wrist placement and shifted to waist placement, we compared associations between PA measures derived from different accelerometer locations with a responsive arterial health indicator, carotid-femoral pulse wave velocity (cfPWV).

Design: Cross-sectional study

Methods: We previously demonstrated an inverse association between waist-worn pedometer-assessed step counts (Yamax SW-200, 7 days) and cfPWV (-0.20 m/s, 95% CI -0.28, -0.12 per 1,000 step/day increment) in 366 adults. Participants concurrently wore accelerometers (ActiGraph GT3X+), most at the waist but the first 46 at the wrist. We matched this subgroup with participants from the 'waist accelerometer' group (sex, age, and pedometer-assessed steps/day) and assessed associations with cfPWV (applanation tonometry, SphygmoCor) separately in each subgroup through linear regression models.

Results: Compared to the waist group, wrist group participants had higher step counts (mean difference 3980 steps/day; 95% CI 2517, 5443), energy expenditure (967 kcal/day, 95% CI 755, 1179), and moderate-to-vigorous-PA (138 mins; 95% CI 114, 162). Accelerometer-assessed step counts (waist) suggested an association with cfPWV (-0.28 m/s, 95% CI -0.58, 0.01); but no relationship was apparent with wrist-assessed steps (0.02 m/s, 95% CI -0.24, 0.27).

Conclusion: Waist but not wrist ActiGraph PA measures signal associations between PA and cfPWV. We urge researchers to consider the importance of wear location choice on relationships with health indicators.

7.2.2 Introduction

Accurate and objective measures of physical activity (PA) and sedentary behavior are needed to study relationships with health metrics. Accelerometers are increasingly used to quantify PA levels in free-living settings and are superior to self report[1].

The recommended and most extensively used accelerometer wear location is the waist, close to the body's center of gravity[1-3]. However, it imposes more participant burden than wrist placement. Waist placement is less convenient with dresses or loosely worn clothing. In recognition of this, the most recently reported cycle (2011-2014) of the National Health and Nutrition Examination Survey (NHANES) switched to placing accelerometers at the wrist[4]. Indeed, preliminary results (2011-2012) from the NHANES study indicated significantly higher adherence rates of 70-80%, compared to 40-70% in previous cycles using waist-worn accelerometers[4].

Our recent experiences in our Step Monitoring to improve ARTERial health (SMARTER) trial also faced decisions related to a balance between participant burden

and accuracy. SMARTER examined the effects of step count prescriptions on arterial health in adults with type 2 diabetes mellitus and/or hypertension[5,6]. The primary PA measure was step counts derived from simple Yamax-200 pedometers worn at the waist (i.e., closing of circuit with hip flexion) and similar devices were used for the intervention. The primary outcome was carotid-femoral pulse wave velocity (cfPWV), a composite indication of arterial health. Participants also wore an ActiGraph GT3X+ accelerometer to capture PA intensity. The first 46 participants wore the accelerometer at the wrist. However, because of poor correlation between accelerometer step counts and pedometer step counts, the remaining 280 participants wore the accelerometer at the waist. At baseline, we demonstrated an association between pedometer-assessed step counts and cfPWV[7]. These findings are in line with the established association of higher step counts with lower incidence of cardiovascular disease events[8]. SMARTER offers an opportunity to compare wrist and waist accelerometer locations in terms of associations of PA measures with a robust measure of arterial health. cfPWV is considered the "gold-standard" measure of arterial stiffness, and an independent predictor of cardiovascular events and mortality[9].

While previous studies have compared the impact of wear location (wrist vs. waist) on step counts[3], activity counts[10,11], and energy expenditure (EE)[12-14] in free-living and laboratory settings, this is the first study to our knowledge that has considered the impact of wear location on the association between PA and an arterial health indicator.

7.2.3 Methods

The present analysis includes a subgroup of participants from the 366 individuals evaluated for the SMARTER trial (Clinicaltrials.gov NCT01475201). Written informed consent was obtained and SMARTER trial procedures were approved by McGill

University's Faculty of Medicine Institutional Review Board (A08-M76-11B) and participating institutions (McGill University Health Centre, St. Mary's Hospital, Jewish General Hospital, Institut de recherches cliniques de Montréal).

Our trial protocol is registered[5], baseline characteristics have previously been described[7], and the final results have been published[6]. Participants were recruited through McGill- and Université de Montréal-affiliated primary care clinics in Montreal, Quebec. Eligibility criteria included diagnosis of type 2 diabetes mellitus and/or hypertension, body mass index (BMI) between 25 and 40 kg/m^2, age of 18 years or older, and absence of any acute or chronic co-morbid conditions affecting ability to walk.

cfPWV was measured non-invasively using applanation tonometry (SphygmoCor, AtCor Medical, Sydney, Australia). Detailed methods have been described previously[5]. Pedometers (Yamax SW-200, San Antonio, TX, USA) with a concealed viewing window were worn at the waist for the assessment of step counts in all participants. This Yamax SW-200 model uses a coiled spring-suspended lever arm requiring 0.35g vertical acceleration for step detection. This device was also used for monitoring by participants and physicians in the active arm which included physician-delivered step count prescriptions.

In addition, at baseline, participants wore research-grade accelerometers were used (ActiGraph GT3X+, Pensacola, FL, USA) not only for the assessment of step counts but also for EE, sedentary time, light PA, moderate-to-vigorous PA (MVPA), and activity counts per minute. Participants (n=46) were initially instructed to wear the accelerometer for 7 consecutive days on the non-dominant wrist at all times (24 hours/day). The subsequent 280 participants were instructed to wear the accelerometer for 7 consecutive days on the waist during waking hours. In both cases, participants removed the accelerometer during bathing and water activities.

Analyses were conducted in participants who wore the accelerometer for ≥10 hours/day for at least 4 out of the 7 days to ensure accurate assessments. Non-wear time was defined as 60 consecutive minutes of zero activity counts, and the spike tolerance was set to 2 minutes of >100 activity counts. The Freedson adult 1998 energy estimation equation was applied[15], and PA levels were classified using cut points previously used in a similar population of older sedentary adults (sedentary: <200 counts/min, light: 200-1,999 counts/min, moderate: 2,000-3,999 counts/min, vigorous: ≥4,000 counts/min)[16]. The data were processed in 10-second epochs using the ActiLife software version 6.5.4. The low frequency extension (LFE) function was not applied to the data presented herein. While, the LFE function may be useful in elderly populations or individuals with very slow walking speeds, we found it led to much higher estimates of step counts in our population. Step counts recorded with the LFE function were greater than with the default filter by 8017 (SD 1939) steps/day [wrist: 8293 (SD 1603), waist: 7694 (SD 2203)].

The 46 participants who wore the accelerometer at the wrist were individually matched with participants from the larger group (n=280) who wore the accelerometer on the waist. Specifically, they were first matched based on sex to ensure a similar sex distribution in the two groups. Participants were then matched for walking levels using pedometer-assessed step counts. They were subsequently matched for age and waist circumference (when possible), two correlates of cfPWV in this cohort. When there was more than one potential match, the participant with the closest pedometer-assessed step counts was selected (within 500 steps/day).

Descriptive statistics were used to summarize participant characteristics using mean, standard deviations (SD), number and proportions, as appropriate. Mean differences between wear location (wrist minus waist) for step counts, EE, light PA, MVPA and

sedentary time were computed with 95% confidence intervals (CIs). Accelerometer wear time was included as a covariate in the models to account for differences in wear time between the wrist and waist locations. Linear regression models were used to evaluate the association between cfPWV and step counts, as well as other accelerometer-assessed PA measures (EE, light PA, MVPA, sedentary time, and activity counts per minute). Our previous examination of the relationship between pedometer-assessed step counts and cfPWV among the full cohort of 366 SMARTER participants included adjustments for several covariates and possible confounding variables. Taking into consideration the smaller sample size in this study, we have presented unadjusted regression coefficients to allow comparison between the subsample of matched participants and full SMARTER cohort. SAS version 9.3 was used (SAS Institute, Cary, NC, USA). Finally, we examined associations between all available accelerometer-derived PA measures and cfPWV for all participants with an accelerometer placed at the waist.

7.2.4 Results

Participants in waist and wrist subgroups were very similar in terms of age, sex, anthropometric measures, and cfPWV (Table 1).

Table 1. Characteristics, Objectively-assessed Step Counts, Physical Activity and Sedentary Time of Waist and Wrist Matched Participants

	Waist Placement Subgroup (n=46)	**Wrist Placement Subgroup (n=46)**	**Wrist vs. Waist** Mean Difference (95% CI)
Participant Characteristics Mean (SD)			
Age, years	60.7 (10.4)	61.1 (12.8)	0.4 (-4.4, 5.3)
Women, no (%)	28 (60.9)	28 (60.9)	-
BMI, kg/m^2	30.9 (4.2)	31.4 (3.5)	0.5 (-1.1, 2.0)
Waist, cm	101.1 (9.5)	97.5 (9.0)	-3.6 (-7.4, 0.3)
Hip, cm	108.7 (9.3)	109.2 (7.9)	0.5 (3.0, 4.1)
Waist:hip	0.9 (0.1)	0.9 (0.1)	0.0 (-0.1, 0.0)
cfPWV, m/s	9.6 (2.1)	9.8 (2.1)	0.2 (-0.7, 1.0)
Pedometer Mean (95% CI)			
Step counts (steps/day)*	5236 (4556, 5917)	5211 (4530, 5891)	-26 (-988, 937)
Accelerometer Mean (95% CI)			
Step counts (steps/day)	6312 (5441, 7182)	10292 (9420, 11186)	3980 (2517, 5443)
Energy expenditure (kcal/day)	445.3 (319.3, 571.3)	1412.2 (1286.2, 1538.2)	966.9 (755.2, 1178.6)
Sedentary activity (hours)	12.2 (11.9, 12.6)	8.2 (7.8, 8.6)	-4.0 (-4.7, -3.4)
Light physical activity (hours)	2.7 (2.4, 3.0)	4.4 (4.2, 4.7)	1.7 (1.3, 2.2)
MVPA (minutes)	24.5 (10.1, 38.8)	162.1 (147.8, 176.4)	137.6 (113.5, 161.7)
Activity counts per minute	389 (246, 531)	2209 (2066, 2352)	1820 (1581, 2060)

BMI, body mass index; cfPWV, carotid-femoral pulse wave velocity; CI, confidence interval; kcal, kilocalorie; MVPA, moderate-to-vigorous physical activity
Accelerometer measures are adjusted for wear time.
*Pedometers were worn at the waist in both subgroups.

The waist and wrist subgroups had similar pedometer-assessed step counts (worn at the waist in both groups) (Table 1). However, in terms of accelerometer measures, participants who wore the accelerometer at the wrist had higher accelerometer-assessed step counts, total activity counts per minute, light PA, MVPA and EE, compared to the subgroup who wore it at the waist (Table 1). The wrist accelerometer location subgroup also recorded less sedentary time than the waist subgroup (Table 1).

In the full cohort of SMARTER participants, we previously reported that a 1,000-step/day increment in walking was associated with a 0.2 m/s (95% CI -0.28, -0.12) decrement in cfPWV in unadjusted analyses, and a 0.1 m/s (95% CI -0.20, -0.02) decrement in cfPWV across models adjusted for several covariates including age, sex, BMI, ethnicity, immigration status, employment, education, diabetes, hypertension, and medication use[7]. The two subgroups examined in the present analyses (accelerometer at wrist and matched group with accelerometer at waist) demonstrated similar relationships between Yamax pedometer-assessed steps and cfPWV in unadjusted analyses as that reported in our full cohort, despite a much smaller sample size in the subgroups (Table 2; Figure 1). However, when the relationships between accelerometer-assessed step counts and cfPWV were examined, a null relationship was apparent for the wrist location (0.02 m/s, 95% CI -0.24, 0.27) while there was a signal for an association with cfPWV for the waist location (-0.28 m/s, 95% CI -0.58, 0.01) (Table 2; Figure 1).

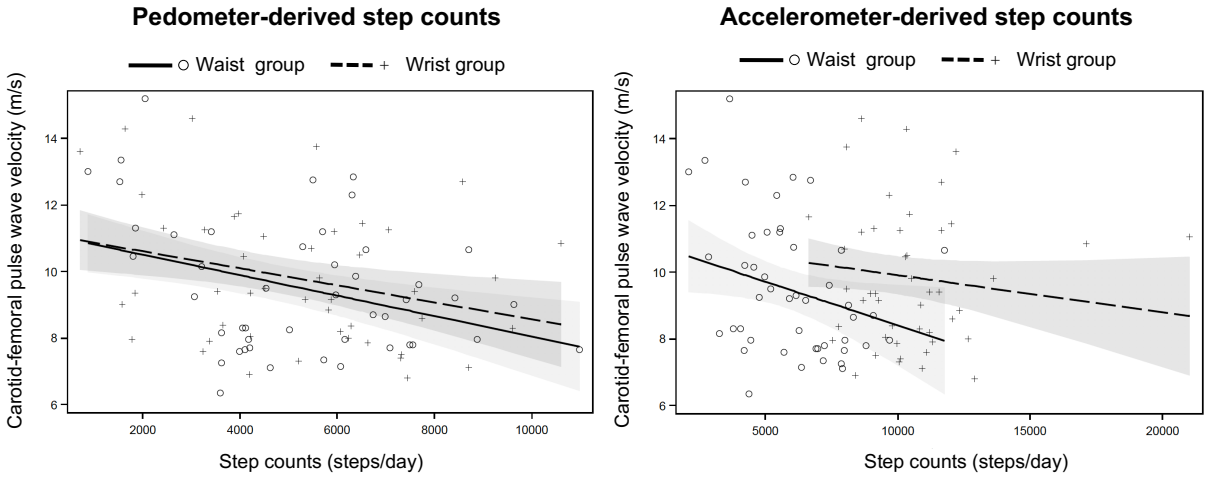
Table 2. Evaluation of the Relationship between cfPWV and Step Counts (Pedometer and Accelerometer-assessed), Energy Expenditure, Sedentary Time, and Physical Activity Levels by Wear Location

	Waist Placement cfPWV change, m/s (95% CI)		Wrist Placement cfPWV change, m/s (95% CI)
	All N=276*	Matched Subgroup N=46	Matched Subgroup N=46
Per 1,000 pedometer-assessed steps/day	-0.20 (-0.28, -0.12)[a]	-0.30 (-0.55, -0.04)	-0.24 (-0.50, 0.01)
Per 1,000 accelerometer-assessed steps/day	-0.20 (-0.30, -0.10)[b]	-0.28 (-0.58, 0.01)	-0.02 (-0.24, 0.27)
Per 100 kcal/day of EE	-0.16 (-0.28, -0.04)	-0.37 (-0.72, 0.03)	-0.05 (-0.18, 0.09)
Per hour of sedentary activity	0.29 (0.08, 0.49)	0.14 (-0.33, 0.61)	0.03 (-0.24, 0.31)
Per hour of light PA	-0.52 (-0.87, -0.18)	-0.10 (-0.90, 0.70)	-0.07 (-0.95, 0.82)
Per 10 minutes of MVPA	-0.24 (-0.36, -0.11)	-0.26 (-0.59, 0.69)	-0.00 (-0.12, 0.12)
Per 100 activity counts per minute	-0.29 (-0.42, -0.15)	-0.32 (-0.66, 0.02)	-0.02 (-0.14, 0.09)

cfPWV, carotid-femoral pulse wave velocity; CI, confidence interval; kcal, kilocalorie; EE, energy expenditure; MVPA, moderate-to-vigorous physical activity
*A larger number of participants wore pedometers (N=366)
[a]When adjusted for age, sex, BMI, ethnicity, immigration status, employment, education, diabetes, hypertension, medication classes: 0.10 m/s (95% CI -0.20, -0.02)[7]
[b]When adjusted for age, sex, BMI, ethnicity, immigration status, employment, education, diabetes, hypertension, medication classes: -0.06 m/s (95% CI -0.15, 0.03)[7]

When we examined all 276 individuals with waist accelerometer location, we identified conclusive relationships between cfPWV and other accelerometer-assessed measures of PA, including EE, sedentary activity, light PA, MVPA, and activity counts per minute (Table 2). In the subgroup analysis, activity counts per minute and EE suggested possible correlations with cfPWV with the waist location, but not the wrist location (Table 2).

Figure 1. Relationship between Pedometer- and Accelerometer-assessed Step Counts and cfPWV by Wear Location



cfPWV, carotid-femoral pulse wave velocity
Shaded area represents 95% confidence interval

7.2.5 Discussion

To our knowledge, our study is the first to compare wrist vs. waist accelerometer wear location in terms of associations with cfPWV, a robust indicator of arterial health and predictor of cardiovascular disease events[9]. The association between accelerometer assessed steps and cfPWV emerged with waist location but not with wrist location. PA measures at the wrist were consistently higher than at the waist. When all participants with waist worn accelerometers were examined, we identified conclusive relationships not only for steps and cfPWV, but also for EE, light PA, MVPA, and activity counts per minute. Thus despite the convenience of the wrist location, our findings further support waist location of accelerometers in research, at least for the ActiGraph GTX model, the most commonly used research grade accelerometer.

Accurate and reliable estimates of free-living PA are especially important when investigating the association between PA and health outcomes. We previously described

an association between waist-worn pedometer-assessed step counts and cfPWV in a large sample of participants, which suggests a measurable arterial health benefit of increased PA[7]. Jennersjo and colleagues have reported a similar relationship between pedometer-assessed step counts and cfPWV; in patients with type 2 diabetes mellitus, a 1,000-step/day increment at baseline was associated with 0.1 m/s slower progression of cfPWV over 4 years[17]. In smaller subsamples in the current study, there was a comparable trend for association between waist-worn pedometer-assessed step counts and cfPWV. This relationship was similar between accelerometer-assessed step counts and cfPWV when the accelerometer was worn at the waist. However, any indication of an association between cfPWV and step counts was lost in the subgroup that wore the accelerometer at the wrist.

In the present analyses, we also demonstrated relationships between cfPWV and other widely used accelerometer-derived measures of PA including EE, light PA, MVPA, and activity counts per minute in the larger group of 276 participants who wore an accelerometer at the waist. Although the associations were not conclusive in the smaller subsamples, we demonstrated stronger associations between cfPWV and EE, sedentary activity, light PA, MVPA, and activity counts per minute with waist placement, compared to wrist placement. Overall, these findings indicate that for ActiGraph monitors, waist-based measurements more accurately reflect the relationship between PA measures and arterial health.

The location-specific differences in associations with arterial health that we have observed can likely be attributed to the imprecise estimates of PA observed at the wrist. Step counts derived from the wrist-worn accelerometer were almost 4,000 steps/day greater than the waist-worn accelerometer. Even though we used ActiGraph's "worn on wrist" option that scales down activity counts at the wrist location, estimated EE

measured in the subgroup with the wrist-worn accelerometer was almost 1,000 kcal higher than the waist subgroup. Moreover, activity counts per minute, a metric that does not depend on cut points or EE prediction equations, was more than 5 times greater in the wrist-worn accelerometer subgroup.

To our knowledge only two other studies have examined the impact of accelerometer wear location on step counts[3]. Tudor-Locke and colleagues compared step outputs obtained from the ActiGraph GT3X+ worn simultaneously on the wrist and waist in laboratory and free-living conditions in 15 young healthy adults. At the wrist, the accelerometer underestimated step counts on the treadmill, but overestimated step counts in free-living conditions: 9,301 (SD 2,887) steps/day (wrist) vs. 6,743 (SD 2,398) steps/day (waist). Similarly, a free-living assessment of step counts in 94 older women also reported markedly higher ActiGraph GT3X+ derived step counts at the wrist compared to the waist: 10,107 (SD 2,785) vs. 5,378 (SD 2,269) steps/day[18]. We noted a difference of 3980 accelerometer-assessed steps/day between the wrist and waist, despite comparable pedometer-assessed step counts measured at the waist. If we consider Tudor-Locke's suggested cut points for categorizing pedometer-determined PA activity, placement of the accelerometer at the wrist misclassifies "low-active" individuals as "active"[19]. The clinical relevance of step counts is being increasingly examined in various research settings, and such inaccuracies limit the comparability of studies, as well as the accuracy of the conclusions.

Other studies have also compared the measurement accuracy of various wear locations, including the waist, wrist, chest, and ankle on other estimates of PA[3,10,11,13,14,20-26]. Using indirect calorimetry as a reference, studies have reported a more accurate estimation of EE at the waist compared to other locations[11-14,21,24]. Rosenberger and colleagues have shown that accelerometers worn at the wrist does not correctly classify

activities into sedentary, ambulation, and MVPA categories[13]. Chen and colleagues also demonstrated an overestimation of EE with respect to whole-room indirect calorimetry when using a wrist-worn accelerometer during low-intensity activities of daily living [14]. These location-specific differences are thought to be largely due to significant arm movement during sedentary activities, or other arm-dominant activities.

These previous studies demonstrate less accurate overall EE with wrist location; they do not, however, speak directly to the relative importance of arm movements vs. whole body movements. Movement at the wrist is still a form of activity with potential benefit. However, we have demonstrated that EE captured with an accelerometer worn at the waist more strongly correlated with cfPWV than when worn at the wrist. Free-living activities that involve movement at the waist are more weight bearing and typically result in higher EE than solely upper body movements[14]. However, these differences are not captured by accelerometers. Therefore, it is possible that the popularity of wrist location in younger, more active populations may not be problematic, but in a population of older sedentary to low-active adults, overestimation of EE from non-weight-bearing movements at the wrist may confound the relationship between EE and arterial health.

Our analyses address a reality: researchers are using wrist-worn accelerometers for the assessment of step counts, energy expenditure and PA levels without location-specific cut points or algorithms. Activity recognition through machine learning approaches is being developed to address excess wrist movement during sedentary activities; however, many different algorithms exist and validation studies are still underway[1,25,27,28]. While these newer methods appear to be better at classifying wrist-derived activity, the current lack of consensus on appropriate algorithms, data storage requirements, and complexity of data processing has prevented their uptake in clinical research. Furthermore, while many algorithms are developed using semi-structured activities in the lab, this may not

translate to free-living settings[29]. For example, Sasaki and colleagues have demonstrated that laboratory-trained algorithms perform poorly when assessing free-living physical activity in older adults. The inclusion of both laboratory and free-living data for training the algorithms improved accuracy, but still did not meet acceptable standards when assessing free-living PA[29]. It is also important to consider that these wrist-specific algorithms have been developed for the estimation of EE and light, moderate, and vigorous PA levels; however, no algorithms exist for step counts. Other non-machine learning methods, such as the GGIR open source package have been developed to process and analyze wrist-derived activity using raw acceleration signals. However, these methods were developed using the GENEA and GENEActiv accelerometers and have not been validated with ActiGraph devices. A comparison of derived GGIR outputs from ActiGraph and GENEActiv accelerometers demonstrated significant differences in the magnitude of overall activity level, and time spent in sedentary to light activity[30].

Our original study was not specifically designed to compare accelerometer wear location, and therefore we acknowledge certain limitations of our approach. For example, since participants were only assessed with either the wrist or waist accelerometer, we were not able to perform a within-participant comparison of the two locations, as other studies have done previously[3,13,24]. However, participant matching generated two comparable groups, and matching for pedometer-assessed step counts at the waist enabled us to compare differences in accelerometer outputs between the two locations, independently. Our evaluation of the impact of wear location on the relationship between step counts and cfPWV is limited by the small size of the wrist and waist subgroups, as we were not able to adjust for the same covariates previously included in the model for our larger SMARTER trial[7]. However, our purpose in this analysis was not specifically to

describe the relationship between step counts and cfPWV, but rather to demonstrate how wear location could impact the relationship.

7.2.6 Conclusions

Our findings add to the body of evidence indicating that wrist-worn accelerometers misclassify PA levels, and that waist-based algorithms are not suitable for assessing wrist-derived activity. We are the first to demonstrate that using ActiGraph derived outputs from a wrist-worn accelerometer may compromise the assessment of the relationship between an arterial health indicator and PA. In general, we would advise against wrist wear locations of devices lacking validated wrist-based algorithms. This is especially important to consider in a sedentary population among whom arm movement likely exceeds total body movement. Therefore, as technology evolves and until more standardized machine learning or raw data methods are developed to accurately capture PA levels via wrist-worn accelerometers, we urge other researchers to be wary of the limitations of using accelerometer-derived outputs from accelerometers worn at the wrist when developing their own study protocols, but also when evaluating clinical studies that have utilized wrist devices.

7.2.6 Acknowledgements

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7.2.7 Conflicts of Interest

None.

7.2.8 References

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7.3 Preamble – Manuscript 6

The work presented in Manuscript 5 focused on methodological considerations for the measurement of physical activity using accelerometers. We showed that the wear location (wrist versus waist) impacts physical activity estimates and that the waist location has a stronger association with cfPWV. These discrepancies have important consequences for the interpretation of research findings and limit the comparability of studies that have used different wear locations. Similarly, different approaches have been adopted in the literature for collecting a reliable measures of arterial stiffness. All studies at the Vascular Health Unit, including the SMARTER and PEDAL trials, have followed the same protocol: measurements of arterial stiffness were repeated until two measures were within 0.5 m/s and reported the average value. The American Heart Association released a scientific statement on the standardization of arterial stiffness measurement in 2016, which suggests reporting the average of at least two cfPWV measurements; if the difference exceeds 0.5 m/s, a third measurement should be taken, and the median reported (a decision based solely on expert consensus)[33]. However, some groups report the average of two readings, irrespective of the distance between them. I was interested in evaluating the impact of these different measurement approaches on the reported cfPWV value. To address this research question, I capitalized on a large amount of arterial stiffness data from five studies at the Vascular Health Unit, which included 27,993 raw PWV datapoints. Through coding in SAS, I was able to isolate measurements of interest (cfPWV), remove poor quality recordings, and identify the reported cfPWV based on the 3 different methods. This study is currently under revision by the *Journal of Hypertension*.

7.4 Content – Manuscript 6

Methodological Considerations for the Measurement of Arterial Stiffness using Applanation Tonometry

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7.4.1 Abstract

Introduction: Accurate comparisons of carotid-femoral pulse wave velocity (cfPWV) within and across studies require standardized procedures. Guidelines suggest reporting the average of at least two cfPWV measurements; if the difference exceeds 0.5 m/s, a third measurement should be taken, and the median reported. Another method involves repeating measurements until two values are within 0.5 m/s. However, in many studies, duplicate measurements are averaged irrespective of the difference between readings. We evaluated the impact of these methods on the reported cfPWV value.

Methods: Measurements of cfPWV (SphygmoCor) from five studies included individuals spanning a wide age range, ±co-morbid conditions, and pregnant women. In participants with ≥3 high-quality measurements, differences between the median value (MED) and (a) the average of the first two cfPWV measurements (AVG1) and (b) the average of two cfPWV measurements within 0.5 m/s (AVG2) were evaluated using paired T-tests and Bland-Altman plots.

Results: Participants' mean age was 50±14 years and BMI was 28.0±5.5 kg/m^2 (N=306, 79% women). The overall mean difference was -0.10 m/s (95% CI 0.17, -0.04) between MED and AVG1, and 0.11 m/s (95% CI 0.05, 0.17) between MED and AVG2. The absolute difference exceeded 0.5 m/s in 34% (MED-AVG1) and 22% (MED-AVG2) of participants, and 1 m/s in 8% of participants (both MED-AVG1 and MED-AVG2). Scatter around the bias line increased with higher mean cfPWV values.

Conclusions: Although the overall mean difference in cfPWV between protocols was not clinically relevant, large variation led to absolute differences exceeding 0.5 m/s in a large proportion of participants.

7.4.2 Introduction

A growing number of researchers and clinicians are evaluating arterial stiffness because of its recognized value as a prognostic indicator of cardiovascular health and arterial aging [1]. Accelerated stiffening of the large arteries is a precursor for isolated systolic hypertension and a widened pulse pressure, which increases the load on the heart and target-organs [1]. Importantly, measurement of arterial stiffness in the central arteries can improve cardiovascular disease (CVD) risk classification, and has an independent predictive value for future cardiovascular events and mortality, even after adjusting for traditional CVD risk factors, including blood pressure[2-5].

The gold-standard metric of central arterial stiffness is carotid-femoral pulse wave velocity (cfPWV)[2-4], with greater cfPWV values reflecting higher aortic wall stiffness[2-4]. Applanation tonometry is widely used for measuring cfPWV[1]. The technique is non-invasive, reliable, and relatively simple to perform by a trained operator.

Accurate comparisons of cfPWV within and across studies require standardized procedures. American Heart Association (AHA) guidelines recommend averaging at least two measurements[1]. If the difference exceeds 0.5 m/s, a third measurement should be taken, and the median value reported[1]. Alternatively, another proposed measurement protocol involves repeating recordings until two values are within 0.5 m/s [6-9]. Nevertheless, in many published reports, duplicate measurements are averaged irrespective of the difference between them. Studies evaluating the impact of these different methods on the reported arterial stiffness value have not been conducted. Therefore, we aimed to evaluate the impact of different methods on the reported cfPWV value in a variety of populations.

7.4.3 Methods

Ethical Approval

Data for this analysis had been previously collected for five studies, for which ethical approval was obtained by either the McGill University Health Centre (MUHC), the McGill University's Faculty of Medicine Institutional Research Ethics Board or the Concordia University Research Ethics Board. Informed consent was obtained from all participants. We subsequently obtained ethical approval for the secondary analyses included herein.

Participants

The study population consisted of participants enrolled in five studies at the Vascular Health Unit (Montreal, QC, Canada), including young healthy individuals [Quantification of the effect of SMOKing on artEriaL stiffnESS (SMOKELESS), Study A][9], overweight/obese young healthy individuals [Acute and Chronic Effects of Obesity (ACEO), Study B], women with high-risk singleton pregnancies assessed during the first trimester [The pRedictivE Value of artErial stiffness in pre-eclAmpsia deveLopment (REVEAL), Study C], middle-aged healthy post-menopausal women [The Effect of Dietary Calcium Intake as Compared to Calcium Supplementation on Vascular and Bone Health in Postmenopausal Women (CALCIUM)[10], Study D], and overweight/obese adults with type 2 diabetes mellitus (T2DM) and/or hypertension [Step Monitoring to improve ARTERial health (SMARTER), Study E][11]. Participants with an arrhythmia that precluded the accurate measurement of arterial stiffness were ineligible for all studies.

Measures

Measurements of cfPWV were performed using applanation tonometry (SphygmoCor CvMS, AtCor Medical, Sydney, Australia) in a supine position. All assessments were conducted by trained operators and a standardized protocol was followed. Participants were asked to refrain from caffeine, alcohol, and smoking at least 5 hours before the assessment, and were instructed to remain still and avoid talking or falling asleep during the assessment[9,12]. Carotid and femoral arterial waveforms were captured separately and synchronized with the R-wave of the electrocardiogram recording. The foot of each waveform was identified by the SphygmoCor software for the calculation of transit time between the two recording sites. The distance between sites was measured using a tape measure, by subtracting the distance between the sternal notch and the carotid site from

the distance between the femoral site and sternal notch. cfPWV was then calculated as the distance divided by the transit time (m/s). Measurements with a pulse transit time standard deviation (SD) >10% and heart rate difference >5 beats/min between carotid and femoral sites were considered poor quality and not included. In all studies, measurements were repeated until two good quality cfPWV measurements were within 0.5 m/s of each other. The arterial stiffness data were collected by different operators, all of whom underwent rigorous training at the lab and a minimum of 10 practice assessments were completed after training to qualify them for clinical assessments.

To evaluate whether differences in the reported cfPWV value between methods led to a reclassification of PWV as normal or abnormal, we used the 'normal' values for cfPWV that were established using data from 1,455 individuals collected from 13 European centres[13]. Given the progressive increase in cfPWV with age, the median cfPWV and the 10th and 90th percentile was reported for each age decade, which has been accepted as reference values for cfPWV[13]. We fitted a quadratic equation to the 90th percentile value from each age range, and calculated the 90th percentile at each age ($PWV = a \times age^2 \times b \times age + c$). We considered this to be the maximum normal value, and used this value to determine whether the reported cfPWV for a particular individual was normal or abnormal.

Blood pressure was measured in a supine position, either using an automated oscillometric blood pressure monitor (BpTRU, Medical Devices Ltd, BC, Canada) (Study B, D, E) or manually using the auscultatory method (Study A and C). Three measurements were taken in all participants. The first reading was discarded, and the subsequent two readings were averaged.

Sociodemographic information, smoking history, past medical history, and medication use was obtained from all participants using a questionnaire. In studies C and E, past medication history and medication use was confirmed by the participant's treating physician.

Statistical Analyses

Main Analysis

Baseline characteristics are summarized for the study total population, as well as for the individual studies, and reported as mean (SD) or number (%), as appropriate. For analyses, studies A and B in young healthy individuals were combined due to similar inclusion criteria. In participants with ≥3 high-quality measurements, paired T-tests and Bland-Altman plots were used to evaluate mean differences in the median value (MED) and 1) the average of first two measurements (AVG1) or 2) average of two measurements within 0.5 m/s (AVG2). The absolute difference between methods was positively skewed, and thus assessed using the non-parametric Wilcoxon Rank Signed test. Correlates of the absolute difference between methods were evaluated using Spearman Rank's correlation. Additionally, within-person reproducibility between single measurements using the first 3 good quality measurements was assessed using the coefficient of variation and intra-class correlation coefficient.

The Kruskal-Wallis one-way analysis of variance was used to evaluate whether the absolute differences between methods varied across operators, specifically comparing the 5 operators who performed the majority of the arterial stiffness assessments (>10%). All other operators performed less than 5% of the tests and were grouped together for the purposes of this analysis.

Exploratory Analysis

The white coat effect, a phenomenon whereby an individual's blood pressure reading is higher when obtained in a medical setting has been a concern for blood pressure measurement[14]. As a result, clinical guidelines recommend discarding the first recorded value to reduce this effect. In an exploratory analysis, we aimed to assess whether the white coat effect exists for arterial stiffness. Among participants with at least 2 good quality cfPWV values, whose first value met all quality control parameters, mean differences between the first and second cfPWV values were evaluated using a paired T-test. We further evaluated mean differences between the first and second cfPWV values in a subgroup of participants whose first systolic or diastolic blood pressure reading was ≥5 mmHg higher than the second measurement. While a difference of 10 mmHg would have been more aligned with the definition of a white coat effect for blood pressure, we used a threshold of 5 mmHg as this value provides a clinically relevant difference and to ensure adequate sample size for this analysis[14]. The first blood pressure reading was not available in Study E, which prevented this analysis in older individuals with T2DM and/or hypertension. We also explored the white coat effect in the participants from our main analysis (i.e., required ≥3 measurements), excluding those with the very first measurement being of poor quality.

Statistical analysis was performed using SAS version 9.3 (SAS Institute, Cary, NC, USA).

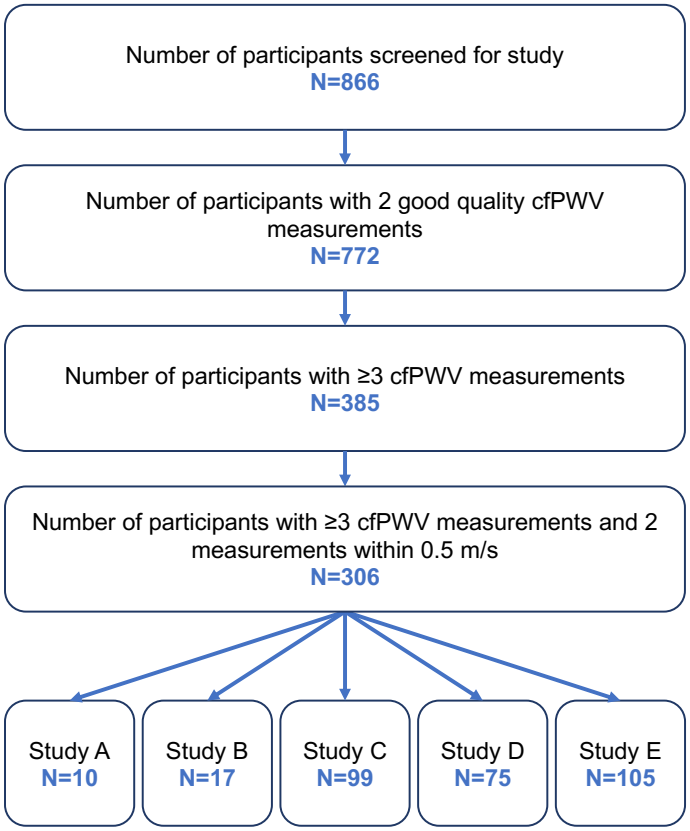
7.4.4.Results

Main Analysis

The 5 studies included 866 individuals. As mentioned, the protocol used in each of the studies required that measurements were repeated until two good quality cfPWV

measurements were within 0.5 m/s of each other. Overall, an average of 3.7±2.1 measurements were completed. Of participants with at least 2 good quality cfPWV measurements (n=772), 51% required ≥3 cfPWV measurements, and were eligible for our main analysis (Figure 1).

Figure 1. Participant Flowchart



cfPWV, carotid-femoral pulse wave velocity

Participants with ≥3 cfPWV measurements were older and had higher cfPWV values than excluded participants whose first 2 values differed less than 0.5 m/s (Supplementary Table 1). A greater proportion of participants with ≥3 cfPWV measurements had hypertension, and were treated with anti-hypertensive agents and

lipid-lowering medications. Of participants with ≥3 cfPWV measurements, we subsequently excluded participants who did not have 2 good quality measurements within 0.5 m/s (n=79). The methods comparison was conducted in the remaining 306 participants. A more detailed summary of participant flow for each study can be found in Supplementary Table 2.

Participants across a wide age range were included (20 to 82 years; mean 50 (SD 15) years) (Table 1). The proportion of women was higher because of the target population of two studies from which data were derived. Participants had an average body mass index of 28.0 kg/m² (SD 5.5, range 16.4 to 48.5 kg/m²). The coefficient of variation for the first 3 good quality cfPWV measurements was 11.3±5.5% and the intra-class correlation coefficient was 0.910 (95% CI 0.891, 0.927).

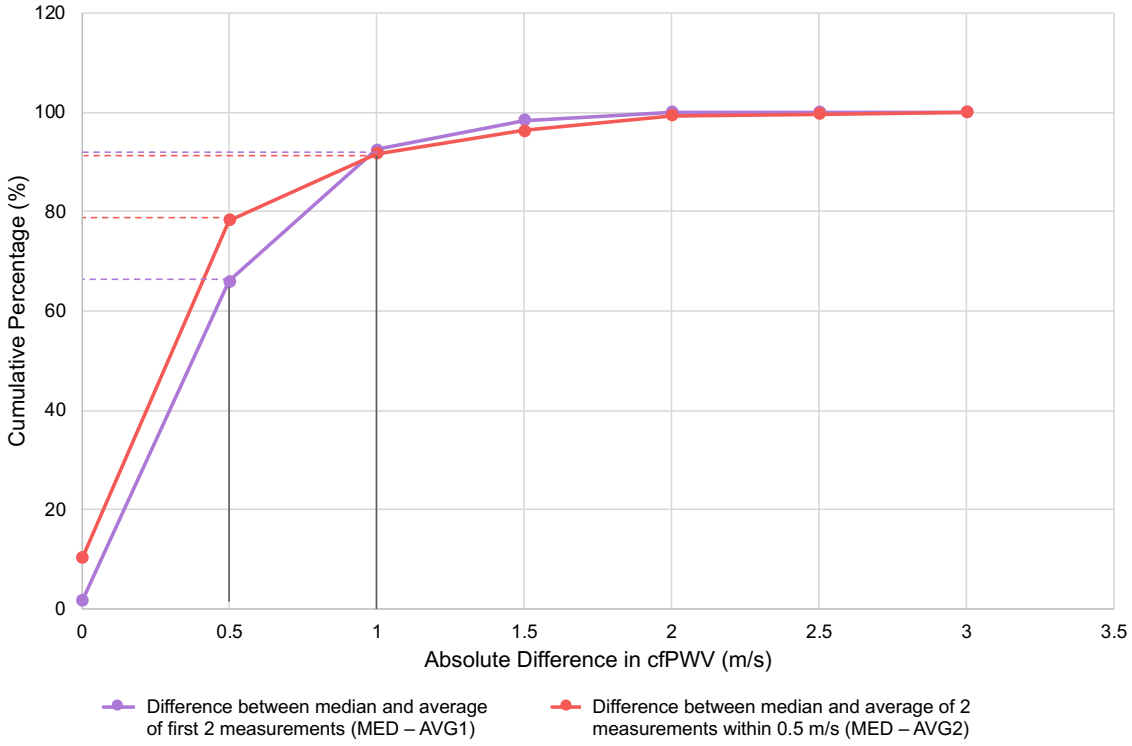
Table 1. Participant characteristics

	OVERALL N=306	STUDY A AND B N=27	STUDY C N=99	STUDY D N=75	STUDY E N=105
Age, years, mean (SD)	49.8 (14.4)	28.9 (4.7)	36.9 (4.2)	60.6 (6.0)	59.6 (10.4)
Sex, % women, no. (%)	243 (79.4)	12 (44.4)	99 (100.0)	75 (100.0)	57 (54.2)
Body mass index (kg/m²)	28.0 (5.5)	29.7 (6.2)	26.2 (5.9)	25.4 (3.4)	31.1 (4.4)
Current smokers, no. (%)	7 (2.3)	3 (11.5)	0 (0)	0 (0)	4 (3.8)
Ethnicity, % White, no. (%)	178 (61.0)	19 (73.1)	36 (40.9)	64 (86.5)	59 (56.7)
Diabetes, no. (%)	73 (24.7)	0 (0)	11 (12.1)	0 (0)	62 (59.1)
Hypertension, no. (%)	98 (33.1)	0 (0)	8 (8.8)	0 (0)	90 (85.7)
Dyslipidemia, no. (%)	71 (23.4)	0 (0)	0 (0)	0 (0)	71 (67.6)
Anti-hypertensive therapy, no (%)	92 (30.3)	0 (0)	2 (2.0)	0 (0)	90 (85.7)
Anti-glycemic therapy, no (%)	71 (23.4)	0 (0)	10 (9.1)	0 (0)	61 (58.1)
Lipid lowering therapy, no (%)	71 (23.4)	0 (0)	0 (0)	0 (0)	71 (67.6)

No., number of participants; SD, standard deviation

The mean difference between MED and AVG1 was -0.10 (95% CI: -0.17, -0.04) m/s (Table 2), and the median absolute difference was 0.40 m/s (IQR 0.25, 0.65; P<0.001 for both). The absolute difference exceeded 0.5 m/s in 34% and 1 m/s in 8% of participants (Figure 2). Overall, the cfPWV classification (normal/abnormal) differed between methods in 10% of participants (n=31; n=14 normal to abnormal, n=17 abnormal to normal).

Figure 2. Cumulative percentage of the absolute difference in carotid-femoral pulse wave velocity (cfPWV) between methods



AVG1, average of first 2 measurements; AVG2, average of 2 measurements with 0.5 m/s; MED, median of first 3 values.

Table 2. Mean differences in carotid-femoral pulse wave velocity (cfPWV; m/s) by study population

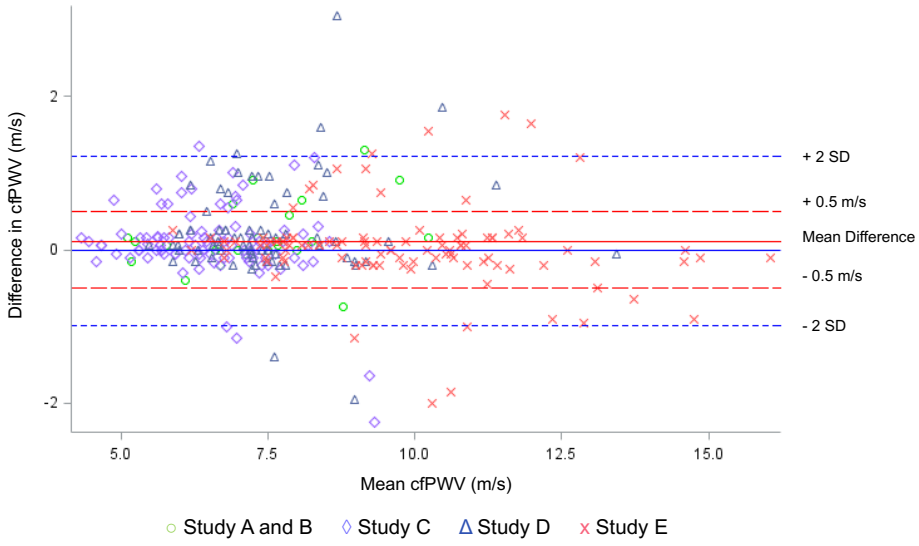
Study Populations	Median of first 3 cfPWV measurements Mean (SD)	Average of first 2 cfPWV measurements Mean (SD)	Average of 2 cfPWV measurements within 0.5 m/s Mean (SD)	Difference between median and average of first 2 cfPWV measurements Mean (95% CI)	Difference between median and average of 2 cfPWV measurements within 0.5m/s Mean (95% CI)
Study A and B Young healthy individuals (n=27)	7.33 (1.37)	7.42 (1.42)	7.18 (1.22)	-0.09 (-0.25, 0.06)	0.15 (-0.01, 0.32)
Study C High-risk pregnant women (n=99)	6.61 (1.01)	6.70 (1.07)	6.53 (1.13)	-0.09 (-0.19, 0.02)	0.09 (-0.01, 0.18)
Study D Healthy post-menopausal women (n=75)	7.62 (1.38)	7.78 (1.31)	7.37 (1.33)	-0.16 (-0.29, -0.03)	0.25 (0.10, 0.40)
Study E Individuals with T2DM and/or HTN (n=105)	9.82 (2.06)	9.90 (1.94)	9.8 (2.13)	-0.08 (-0.21, 0.05)	0.03 (-0.08, 0.13)
Overall (n=306)	8.02 (2.06)	8.12 (2.02)	7.90 (2.12)	-0.10 (-0.17, -0.04)	0.11 (0.05, 0.17)

Legend: carotid-femoral pulse wave velocity; CI, confidence interval; HTN, hypertension; SD, standard deviation; T2DM, type 2 diabetes mellitus

The mean difference between MED and AVG2 was 0.11 (95% CI: 0.05, 0.17) m/s (Table 2) and the median absolute difference was 0.15 m/s (IQR 0.05, 0.30; P<0.001 for both). The absolute difference exceeded 0.5 m/s in 22% and 1 m/s in 8% of participants (Figure 2). The divergence between lines from 0 to 1 m/s in Figure 2 further shows that a larger proportion of participants had a smaller absolute difference between methods when comparing MED and AVG2 versus MED and AVG1. Of note, in 75% of participants the absolute difference between MED and AVG2 was <0.3 m/s. Overall, the cfPWV classification (normal/abnormal) was different between methods in 5% of participants (n=15; n=6 normal to abnormal, n=9 abnormal to normal).

Bland Altman plots also demonstrated large absolute differences between methods (Figures 3 and 4). The limits of agreement (mean difference ± 2SD) were -1.28 and 1.08 m/s for the MED-AVG1 comparison and -0.99 and 1.21 m/s for the MED-AVG2 comparison. In both comparisons, the scatter around the bias line increased with higher mean values of cfPWV.

Figure 3. Agreement between the median cfPWV value (MED) and average of the first two cfPWV measurements (AVG1) by study population



cfPWV, carotid-femoral pulse wave velocity; SD, standard deviation

Figure 4. Agreement between the median cfPWV value (MED) and average of the first two cfPWV measurements within 0.5 m/s (AVG2) by study population

cfPWV, carotid-femoral pulse wave velocity; SD, standard deviation

Higher cfPWV was associated with a greater absolute difference between methods: MED vs. AVG1 (r=0.218, P<0.001) and MED vs. AVG2 (r=0.204, P<0.001). Age was associated with a greater difference in cfPWV between MED and AVG1 (r=0.133, P=0.021). Body mass index, blood pressure, heart rate, and pulse transit time standard deviation were not associated with differences in cfPWV between methods. The absolute difference between methods was similar across operators (P>0.05 for both MED-AVG1 and MED-AVG2).

Exploratory Analysis

Baseline characteristics of participants included in the white coat analysis (first 2 cfPWV measurements that met quality control) is shown in Supplementary Table 3. We did not observe a higher value of the first cfPWV recording in any of the studies, or the overall group (Table 3). We further compared the first and second cfPWV values in a

subset of individuals from Study A-D whose first systolic and/or diastolic blood pressure reading exceeded the second one by 5 mmHg. Despite a higher first blood pressure reading, we did not observe a higher first cfPWV measurement (Supplementary Table 4). In participants with ≥3 cfPWV measurements (main analysis group), we observed a higher first cfPWV value (Table 3). The first cfPWV value also differed significantly from the MED and AVG2 value (Supplementary Table 5).

Table 3. Differences between first and second carotid-femoral pulse wave velocity (cfPWV) measurements

Study Populations	First cfPWV measure	Second cfPWV measure	Mean Difference (First – second)
Study A and B **Young healthy individuals (n=96)**	6.63 (1.30) (95% CI 6.37, 6.89) HR: 61.8 (9.4)	6.54 (1.17) (95% CI 6.30, 6.77) HR: 61.7 (9.5)	0.09 (0.54) (95% CI -0.02. 0.20)
Study C **High-risk pregnant t women (n=148)**	6.51 (1.28) (95% CI 6.30, 6.72) HR: 73.3 (9.7)	6.45 (1.05) (95% CI 6.28, 6.62) HR: 73.4 (9.7)	0.06 (1.16) (95% CI -0 .13, 0.25)
Study D **Healthy post-menopausal women (n=84)**	7.39 (1.24) (95% 7.13, 7.66) HR: 55.2 (8.4)	7.48 (1.35) (95% 7.18, 7.77) HR: 55.4 (8.5)	-0.09 (1.22) (95% CI -0.35, 0.18)
Study E **Individuals with T2DM and/or HTN (n=242)**	9.59 (2.07) (95% CI 9.33, 9.86) HR: 66.0 (11.2)	9.41 (2.10) (95% CI 9.15, 9.68) HR: 66.3 (11.4)	0.18 (1.47) (95% CI -0.01, 0.37)
Overall (n=570)	7.97 (2.19) (95% CI 7.79, 8.15) HR: 65.6 (11.7)	7.88 (2.12) (95% CI 7.70, 8.05) HR: 65.8 (11.8)	0.09 (1.24) (95% CI -0.01, 0.20)
Participants requiring ≥3 cfPWV measurements (n=229)	8.11 (2.27) HR: 66.9 (12.4)	7.88 (1.99) HR: 66.2 (12.4)	**0.23 ± 1.56** **(95% CI 0.03, 0.43)**

All values expressed as mean (SD)
HR, heart rate; SD, standard deviation

7.4.5 Discussion

This study evaluated the agreement between methods currently being applied for calculating cfPWV using applanation tonometry. We focused on the agreement between the median approach, which has been adopted in recent guidelines[1], and the average value from duplicate measurements, where 1) the distance between the measurements is ignored, and 2) the measurements are repeated until two values within 0.5 m/s. Although the overall mean difference between methods was small (±0.1 m/s), large variation led to absolute differences that exceeded 0.5 m/s in up to one third of participants requiring ≥3 cfPWV measurements. Differences of this magnitude between methods could have important clinical implications. For example, a 1 m/s increase in cfPWV is associated with a 15% increased risk of cardiovascular events and mortality as demonstrated in a large meta-analysis (n=15,877 individuals, 17 longitudinal studies)[4]. The importance of aortic PWV in risk stratification has been highlighted in a recent individual participant data meta-analysis (n=17,000), whereby the addition of aortic PWV improved classification of CVD risk over and above traditional risk factors, including blood pressure[3]. Moreover, differences between methods led to a reclassification of PWV as normal/abnormal in 10% and 5% of participants, when comparing the MED value to the AVG1 and AVG2 values, respectively. Therefore, discrepancies in the reported cfPWV value due to methodological differences could re-classify individualized risk for CVD and alter subsequent treatment decisions.

Previous methodological studies related to the arterial stiffness measurement have focused on the reproducibility of the technique. Specifically, a high-level of reproducibility has been shown in studies using the SphygmoCor device, both within- and between-observer, as well as on separate visits[15-19]. Our analysis of the intra-class

correlation coefficient in participants requiring ≥3 cfPWV measurements also showed a high-level of reproducibility. However, despite this, we have demonstrated that different methodologies for collecting the measurements lead to clinically relevant differences.

We observed that the absolute difference between methods was greater at higher cfPWV values. Age was also associated with a greater absolute difference between MED and AVG1; however, this was likely driven by the fact that older subjects had higher cfPWV values. In line with these findings, we also observed that participants who required ≥3 measurements were older than participants whose first 2 measurements were within 0.5 m/s. Therefore, while differences between methods should be considered at all ages, we have shown that this might be even more relevant in older populations. Participants in Study D had greater differences between the MED and AVG1, as well as MED and AVG2 values than other studies, which was driven by a higher second cfPWV value. Similarly, the second cfPWV was higher than the first cfPWV value in participants whose first blood pressure reading exceeded the second by more than 5 mmHg (despite no differences in heart rate), which was not observed for the other studies. Together, these findings may suggest a greater variability in the measurement in this subgroup of middle-aged postmenopausal women; however, we are unaware of a physiological reason and our study was not designed to explore this.

Papaioannou and colleagues previously reported that the average of 2 or 3 successive cfPWV measurements was significantly different from any single value, indicating large variation from one measurement to the next and the need to obtain at a minimum the average of duplicate measurements [20]. The study was completed in 60 older individuals referred for a cardiovascular risk assessment. They demonstrated that substantially different information was provided by average PWV relative to single measurements in

terms of cardiovascular risk estimation and PWV classification (same approach used herein). The difference between any 2 out of 3 single cfPWV measurement replicates corresponded to a difference of 0.5 m/s in 27-38% of subjects. However, the impact of using the median value versus an average was not investigated in this study. Together, our findings highlight the need for a standardized approach. Consistent with the need for a pragmatic attitude, it is reasonable to report the average of the first two measurements if they are within 0.5 m/s. This was the case in 49% of our study participants. However, when the difference between the first two measurements exceeds 0.5 m/s, we would support adopting the median approach, where a 3rd measurement is taken, and the median value be reported. This approach is practical and currently recommended[1,21], as well as feasible in clinical practice, without adding much additional time.

The white coat effect observed with blood pressure is mainly attributed to the activation of the sympathetic nervous system, and previous research has demonstrated that the first blood pressure reading is usually higher than successive readings[22]. Arterial stiffness is influenced by sympathetic activation[23,24] and blood pressure[25], and therefore may be influenced by the white coat effect; however, whether a white coat effect exists for arterial stiffness had not been evaluated. Evidence of a higher first arterial stiffness value would indicate that measuring arterial stiffness should follow a similar protocol to that of blood pressure measurement where the first value is discarded. Our findings from an exploratory analysis of a white coat effect for arterial stiffness indicate that the first cfPWV measurement was not significantly higher than the subsequent value in the overall group. However, we observed a higher first cfPWV value in participants requiring ≥3 cfPWV measurements. These participants were older, had higher cfPWV

and a greater proportion were treated for hypertension. Therefore, this population may tend to have a higher first cfPWV value than younger, healthier populations where the first 2 measurements were more likely to be within 0.5 m/s. However, a study specifically designed to assess white coat arterial stiffness that involves a series of repeated measurements in all participants should be conducted to corroborate our findings. It should also be noted that participants had already undergone measurements of pulse wave analysis and carotid-radial PWV prior to cfPWV measurements. Since cfPWV requires palpation of the femoral artery located in a more sensitive area we were still interested in evaluating whether this would lead to a higher first measure. We also did not observe differences in a subgroup of individuals who had a higher first to second blood pressure reading (≥5mmHg). However, given the influence of blood pressure on cfPWV, it would be worthwhile investigating the magnitude of the cfPWV differences in a larger group of individuals with a more marked blood pressure difference as these individuals might be the most susceptible to a higher initial arterial stiffness measurement.

An important strength of our study is its relatively large sample size which provided adequate power to explore differences between methods, as well as our inclusion of different populations spanning a wide range of age, BMI, and CVD risk. However, an invasive measure was not available, which would have allowed a comparison of the different methods with regard to their accuracy in reporting arterial stiffness values. Similarly, there was no outcome measure that was comparable across studies, thus preventing us from determining the most clinically relevant method. However, we did evaluate the impact of differences between methods on the age-adjusted cfPWV classification as normal or abnormal. Most importantly, the results were specific to the

SphygmoCor Cardiovascular Management System (CvMS) device. Although this is the most widely used device for the measurement of arterial stiffness, our results may not be generalizable to other devices. It is possible that newer less operator-dependent cuff-based devices produce less deviation in terms of arterial stiffness differences between methods. Additionally, we opted to include data collected by a number of different trained operators at the lab to increase the generalizability of our findings and provide data that reflects the reality of other clinical labs, where a number of different operators and study populations would be involved. We verified that that the absolute difference between methods was comparable across operators in our study; however, we acknowledge that multiple operators introduce an added element of variability that may influence the magnitude of the differences in cfPWV between methods.

7.4.6 Conclusion

We have identified important differences between methods for reporting cfPWV, which could result in discrepancies in risk classification for CVD, especially among older participants. We did not observe any obvious white coat effect for arterial stiffness when all participants with 2 or more cfPWV were assessed; however, there was indication of a higher first cfPWV in the subgroup of participants who required more than 3 measurements. This phenomenon should be evaluated further in a study specifically designed to conduct repeated measurements of arterial stiffness in all participants. Future studies with invasive measurements of arterial stiffness and clinical outcomes should also evaluate the most accurate and clinically relevant method for reporting of arterial stiffness indices.

It is important that researchers are transparent in their reporting of arterial stiffness measurements, and methodological differences should be considered when comparing

different studies. Moving forward, standardized protocols should be implemented in all studies. Guidelines, such as the AHA statement[1], and other expert consensus documents [12,21], have likely helped, but continued efforts through journal requirements, conferences and scientific associations is necessary.

7.4.7 Acknowledgements

The studies included in this secondary analysis were supported by the Canadian Institutes of Health Research (CIHR: #130531, #102626, #79285), the Fonds de recherche du Québec-Santé (FRQS: #25045), Heart and Stroke Foundation, the Dairy Farmers of Canada, and the Natural Sciences and Engineering Research Council. ABC has received doctoral funding from CIHR and FRQS. TGP has received equipment from IEM GmbH for research purposes (not relevant to this manuscript) and a grant from State Scholarships Foundation. JM has received doctoral funding from FRQS, and a PERFORM doctoral fellowship. SSD and SNM are supported by a FRQS clinician scientist award. SS is a Canada Research Chair Tier 2 in Clinical Nutrition.

7.4.8 Conflicts of Interest

None to disclose.

7.4.9 References

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7.5 Supplemental Material – Manuscript 6

Supplemental Digital Content 1. Characteristics of participants with 2 first cfPWV measurements within 0.5 m/s and participants with ≥3 cfPWV measurements

	PARTICIPANTS WITH FIRST 2 CFPWV MEASUREMENTS WITHIN 0.5 M/S **N=349**	PARTICIPANTS WITH ≥3 CFPWV MEASUREMENTS **N=385**	P-VALUE
Age, years, mean (SD)	44.1 (15.4)	51.3 (14.8)	<0.0001
Sex, % women, no. (%)	228 (66)	290 (76)	0.002
Body mass index (kg/m^2)	27.7 (6.1)	28.5 (5.6)	NS
Current smokers, no. (%)	43 (13)	12 (3)	NS
Ethnicity, % White, no. (%)	200 (59)	222 (61)	NS
Diabetes, no. (%)	81 (24)	110 (30)	NS
Hypertension, no. (%)	104 (30)	152 (41)	0.004
Dyslipidemia, no. (%)	73 (21)	111 (29)	NS
Anti-hypertensive therapy, no (%)	99 (29)	146 (38)	0.006
Glucose lowering therapy, no (%)	78 (23)	103 (27)	NS
Lipid lowering therapy, no (%)	63 (18)	107 (28)	0.002
Systolic blood pressure, mmHg, mean (SD)	114 (14)	118 (16)	0.018
Diastolic blood pressure, mmHg, mean (SD)	71 (8.4)	72 (10)	0.040
cfPWV, m/s, mean (SD)	7.5 (2.0)	7.9 (2.1)	0.009
Pulse transit time coefficient of variation, %, mean (SD)	6.4 (1.4)	6.4 (1.4)	NS

No., number of participants; SD, standard deviation

Supplemental Digital Content 2. Participant Flow by Study for Main Analysis

	Study A	Study B	Study C	Study D	Study E	Combined
Number of participants screened for study	127	43	207	122	367	866
Number of participants screened for study with 2 good quality cfPWV measurements	106	42	200	116	308	772
Number of participants screened for study with 2 good quality cfPWV measurements within 0.5 m/s	101	42	186	115	290	734
Number of participants with ≥3 cfPWV measurements	10	18	114	78	165	385
Number of participants with ≥3 cfPWV measurements and 2 measurements within 0.5 m/s	10	17	99	75	105	306

cfPWV, carotid-femoral pulse wave velocity

Supplemental Digital Content 3. Characteristics of participants included in exploratory white coat analysis

	Overall group **N=570**	Study A and B **n=96**	Study C **N=148**	Study D **N=84**	Study E **N=242**
Age, years, mean (SD)	48.3 (15.1)	29.2 (6.3)	36.8 (3.9)	60.0 (5.8)	58.7 (11.0)
Sex, % women, no. (%)	397 (71)	45 (49)	148 (100)	84 (100)	124 (52)
Body mass index (kg/m^2)	28.2 (5.8)	26.3 (5.8)	26.0 (6.3)	25.4 (3.8)	31.3 (4.4)
Current smokers, no. (%)	16 (3)	0 (0)	0 (0)	0 (0)	16 (7)
Ethnicity, % White, no. (%)	322 (59)	58 (62)	53 (41)	76 (93)	135 (57)
Diabetes, no. (%)	156 (28)	0 (0)	16 (12)	0 (0)	140 (59)
Hypertension, no. (%)	207 (38)	0 (0)	12 (9)	0 (0)	195 (82)
Dyslipidemia, no. (%)	150 (27)	2 (2)	0 (0)	0 (0)	148 (62)
Anti-hypertensive therapy, no (%)	204 (37)	0 (0)	4 (3)	0 (0)	200 (84)
Anti-glycemic therapy, no (%)	147 (26)	0 (0)	14 (10)	0 (0)	133 (56)
Lipid lowering therapy, no (%)	141 (25)	0 (0)	0 (0)	0 (0)	141 (59)

No., number of participants; SD, standard deviation

Supplemental Digital Content 4. Differences between first and second cfPWV measure in participants with a higher first blood pressure reading

Study Populations	First cfPWV measure	Second cfPWV measure	Mean Difference
Study A and B Young healthy individuals (n=25)	6.95 (1.03) (95% CI 6.52, 7.37) HR: 62.7 (8.4)	6.82 (0.86) (95% CI 6.46, 7.17) HR: 63.1 (8.7)	0.13 (0.68) (95% CI -0.15, 0.41)
Study C High-risk pregnant women (n=13)	6.44 (1.08) (95% CI 5.79, 7.09) HR: 76.4 (9.1)	6.80 (1.02) (95% CI 6.18, 7.42) HR: 77.3 (10.2)	-0.36 (1.10) (95% CI -1.03, 0.30)
Study D Healthy post-menopausal women (n=20)	6.97 (1.37) (95% CI 6.33, 7.61) HR: 58.3 (8.3)	7.60 (1.77) (95% CI 6.77, 8.42) HR: 59.2 (8.0)	-0.63 (1.25) (95% CI -1.21, -0.04)
Overall (n=58)	6.84 (1.17) (95% CI 6.53, 7.14) HR: 64.3 (10.8)	7.08 (1.31) (95% CI 6.73, 7.42) HR : 64.9 (11.1)	-0.23 (1.05) (95% CI -0.51, 0.03)

All values expressed as mean (SD), bolded values indicate significance
cfPWV, carotid-femoral pulse wave velocity; SD, standard deviation

Supplemental Digital Content 5. Differences between a single measurement and the median, AVG1 and AVG2 values

	cfPWV, m/s mean (SD) N=306	**Mean difference from 1st cfPWV measurement**
1st cfPWV measurement	8.21 ± 2.33	-
Average of first 2 cfPWV measurements	8.12 ± 2.02	-0.09±0.88 m/s (95% CI -0.19, 0.01)
Median of 3 cfPWV measurements	8.02 ± 2.06	**-0.19±1.13 (95% CI -0.32, -0.07)**
Average of two measurements within 0.5 m/s	7.90 ± 2.12	**-0.30±1.3 (95% CI -0.45, -0.16)**

Additional Analyses for Manuscript 6

As detailed in the manuscript, to evaluate whether differences in the reported cfPWV value between methods led to a reclassification of PWV as normal or abnormal, we used data presented by The Reference Values for Arterial Stiffness Collaboration. Participants in the reference value population were free from CVD, did not have diabetes, and were not treated with anti-hypertensive or lipid-lowering medications. 'Normal' values for cfPWV were established using data from a subgroup of 1,455 individuals with optimal/normal blood pressure; these values were used for the reclassification analyses presented in Manuscript 6. However, this approach does not consider the participant's blood pressure and uses only the 'normal' values for cfPWV which may not be appropriate in participants with above-normal blood pressure. Therefore, we have additionally performed these reclassification analyses using the 'reference' values for cfPWV that were established using data from the larger group of 11,092 individuals, according to their blood pressure category. A range of blood pressure values was noted in this population and reference values are presented for each blood pressure category (optimal, normal, high-normal, grade 1, grade 2-3). For each blood pressure category, we fitted a quadratic equation to the 90th percentile value from each age range and calculated the 90th percentile at each age ($PWV = a \times age^2 \times b \times age + c$). We considered this to be the maximum normal value and used this value to determine whether the reported cfPWV for a particular individual was normal or abnormal. Overall, the cfPWV classification (normal/abnormal) was different between methods in 8% of participants when we compared the MED-AVG1 and MED-AVG2 values (1) AVG1: n=25; n=8 normal to abnormal, n=17 abnormal to normal, and 2) AVG2: n=23; n=13 normal to abnormal, n=10 abnormal to normal). This aligns with the results in the manuscript which suggested

reclassification occurs in 5-10% of participants. The limitation of this approach is that participants in the reference value population were categorized based on a seated measure of blood pressure, while we have used a supine measure of blood pressure. However, our conclusion remains consistent regardless of the reclassification method used.

CHAPTER 8: General Discussion

8.1 Summary

The overall goal of my work was to evaluate the effectiveness of physical activity interventions integrated into clinical care, with a focus on the arterial health impact and physical activity behavior. Together, the six manuscripts presented in this thesis extend our understanding of the effectiveness of two real-life physical activity interventions integrated into clinical care, provide novel evidence regarding the arterial stiffness and hemodynamic response to acute maximal exercise in adults with T2DM, and address important methodological questions related to physical activity monitoring and arterial stiffness measurement.

Chapter 4 which consisted of *Manuscripts 1 and 2* provided a more in-depth examination of the SMARTER trial, a physician-delivered pedometer-based step count prescription intervention. Given the successful impact of the SMARTER strategy on daily step counts, and improvements in glucose control and insulin resistance, I was interested in exploring factors that influenced the effectiveness of the intervention, from both a quantitative and qualitative perspective. *Manuscript 1* explored barriers and facilitators from patient and physician perspectives. Overall, the strategy components (pedometer, step count prescriptions, log book) were well-received by both participants and physicians. Accountability to physicians, support from the trial coordinator, and the target setting aspect influenced participant motivation. Participants who decreased overall steps reported difficulty in overcoming weather-related challenges, health limitations and work constraints, whereas participants who increased steps developed strategies to overcome these barriers. Physicians indicated that the approach provided a concrete means of discussing and monitoring physical activity but highlighted a need for support to help deliver the strategy in busy clinical settings. In *Manuscript 2* we

demonstrated that trajectories of mean steps/day in response to a 1-year physician-delivered step count intervention among adults with chronic disease were stratified as a function of initial step count levels (sedentary, low active, somewhat active, and active) but all followed an upward slope. Individuals with T2DM and older individuals start at and end at lower absolute steps/day but did not differ from others in terms of changes relative to baseline. These findings indicate that the strategy has the potential to be effective in increasing steps irrespective of baseline counts and other clinical/demographic characteristics. Interestingly, participants who start the intervention during fall/winter may benefit from the intervention to a greater extent. Together, these findings will inform the future implementation of the SMARTER strategy, as well as other physical activity promotion strategies.

Our pilot randomized controlled trial presented in **Chapter 5** demonstrated that pedaling exercise during regular hemodialysis sessions is a safe and realistic means to help patients with CKD achieve the arterial health benefits of increased physical activity. We showed a clinically meaningful reduction in cfPWV, as well as a reduction in heart rate. Blood pressure was lower, but not conclusively. The decrease in cfPWV after pedaling exercise was partially reversed 4 months after exercise cessation, which reinforces the need for maintenance of regular physical activity in this population.

As presented in **Chapter 6**, we incorporated acute maximal exercise as a stressor to evaluate the response of the arteries to increased demands. Our results demonstrated that the cfPWV immediately post-exercise in individuals with T2DM was 1.6 m/s over and above that observed for individuals without T2DM, independently of the higher resting value. The elevated arterial stiffness response was also independent of blood pressure at the time of measurement, suggesting that increased central arterial stiffness during exercise contributes to the exaggerated BP response in participants with T2DM. We

believe this is an important step in understanding the underlying hemodynamic mechanisms of the exaggerated BP response in individuals with T2DM.

Chapter 7 focused on methodological considerations for the assessment of physical activity and arterial stiffness. In *Manuscript 5* we identified differences in ActiGraph-derived physical activity measures between waist and wrist accelerometer locations. These findings were in line with previous reports showing a similar overestimation in physical activity. However, previous work was extended by further identifying important differences in their relationship with cfPWV, a clinically relevant outcome; waist location accelerometer-derived physical activity signaled a relationship with cfPWV, but the wrist location did not. These results add a new element to the evidence base supporting waist as the preferred accelerometer wear location in research and will hopefully inform the future design of studies involving physical activity assessment.

A number of approaches have been adopted in the literature for collecting a reliable measure of arterial stiffness. As presented in *Manuscript 6*, we carried out a study comparing the different approaches currently used; the median of the first 3 values, the average of the first two values, and the average of the first two measures within 0.5 m/s. Although the significant mean difference in cfPWV between protocols was not clinically relevant, large variation led to absolute differences exceeding 0.5 m/s, a clinically relevant threshold, in a large proportion of participants (up to 34%). Moreover, differences between methods led to a reclassification of PWV as normal/abnormal in 10% and 5% of participants, when comparing the median value to the average of the first two values and the average of the two values within 0.5 m/s, respectively. These findings suggest that methodological differences need to be considered when comparing results across studies. Importantly, researchers should be encouraged to follow a standardized protocol for their future studies.

8.2 In Context

Since completing the SMARTER trial, important strides have been made by SMARTER trial investigators to incorporate a formalized step count prescription into clinical practice. The evidence from the SMARTER trial has been integrated into the 2018 Clinical Practice Guidelines, which suggests that physicians "*encourage people with diabetes to self-monitor physical activity with a pedometer or accelerometer. Ask them to record values, review at visits, set step count targets and formalize recommendations with a written prescription*". Moreover, a formal prescription has been appended to facilitate uptake by physicians. In addition to the follow-up work presented in this thesis, a cost-effectiveness analysis has been carried out by the SMARTER group demonstrating that the overall cost of the strategy is low[228]. The additional cost per patient was $101.89 which included the pedometer, additional nursing time, as well as physician training time.

The SMARTER trial has been included in a very recent meta-analysis evaluating the impact of step count interventions with a pedometer or accelerometer on cardiometabolic health[229]. Overall, they assessed 36 studies (5,208 participants) and demonstrated a small to medium effect on physical activity and step counts (1,703 steps/day increase compared to usual care). Interestingly, interventions that integrated regular consultations with health professionals were more effective than self-monitoring only. About a third of the studies included in the review were published in 2017 or later, indicating a continued interest in the field of physical activity monitoring interventions. The results from our qualitative follow-up in *Manuscript 1* and our analysis of step count trajectories over the course of a step count intervention in *Manuscript 2* are relevant to many of the other interventions included in the meta-analysis and could inform the implementation of these strategies into practice. Interestingly, the meta-analysis showed that interventions

that integrated regular consultations with health professionals were more effective than self-monitoring only. These findings further support the integration of a step-count prescription strategy into care. The Exercise is Medicine global initiative has recently made important strides to incorporate time-based physical activity prescriptions into the clinic visit as a standard of care (delivered by the physician)[230]. They have acknowledged the reality that not all physicians can provide the extended behavioral counseling that is often needed, and therefore encourage the involvement of allied health professionals as 'physical activity intervention advisors' who can provide more in-depth counseling and follow-up with patients. Similarly, support from other professionals has been incorporated into New Zealand's 'Green Prescription' initiative, a government-funded physical activity prescription program delivered by health care professionals and integrated into clinical practice[231]. Patients additionally receive telephone or in-person support from a physical activity counselor and group support in a community setting is also offered. The SMARTER physician step count prescription and follow-up approach, on the other hand, aims to continually involve the physician at routine clinic visits, thus ensuring participants receive a formal written prescription from their physician. This type of strategy is well-suited to individuals with T2DM and HTN who are already accustomed to monitoring their glucose and blood pressure levels daily at home, and reporting these values to their physician. The SMARTER strategy focused on the prescription of step counts rather than other activity metrics, which is simple to grasp by physicians and more easily integrated into daily life for patients who may not have access to exercise equipment. However, we acknowledge that additional motivational support may be needed to amplify the effects.

Since the SMARTER trial was started in 2011, considerable progress has been made in the field of physical activity monitoring. Simple waist-worn pedometers are now

equipped with Bluetooth to sync the data automatically to web-based or smartphone applications for simple tracking of step counts. Many pedometers have also replaced the lever arm mechanism and now register steps by the simple movement of a piezoelectric crystal. This enables more accurate step counting in participants with larger waist circumference, as well as slower walking speeds[232]. Importantly, they remain an affordable option for step count monitoring (<$25). Accelerometers are increasingly being used due to their ability to capture information on a number of other physical activity metrics including intensity, duration, sedentary time, and energy expenditure. Several consumer-level options are now available (Fitbit, Garmin, Apple watch, etc.), and are gaining popularity in the general public. The emergence of these simple, accessible, and easy to wear devices has stimulated a general interest in physical activity and health tracking. The adoption of pedometer-based physical activity promotion strategies in clinical practice is very dependent on the participant's willingness to wear a step tracking device every day. Recent technological advances are likely to facilitate this. Furthermore, both patients and their physicians can benefit from real-time monitoring of step count and physical activity trends over time. Several applications have also integrated reminders and motivational messages to encourage users to reach their physical activity targets, as well as group-based challenges. We and others have shown that a prescription approach from the treating physician is effective at increasing physical activity levels and improving health outcomes[15,16,18], but the added support that is now available through virtual apps may further encourage patients in reaching their targets. Technological advances are also reaching the health care system in the form of telemedicine, which is increasingly being adopted in acute and chronic care settings[233]. The coronavirus disease 2019 (COVID-19) pandemic forced an acceleration of its adoption, and will likely change the way healthcare is delivered. As a result, patients will be even more accustomed to

electronic health applications to self-monitor and manage their conditions. This situation provides us with the opportunity to integrate physical activity monitoring and coaching into telemedicine programs, and find innovative solutions that make it easier for physicians to engage patients in non-pharmacological approaches to disease prevention and treatment.

Wearing the accelerometer on the wrist is being increasingly considered in research settings for convenience reasons as well as for sleep monitoring, an expanding area of research[234]. As a result, machine learning algorithms are being developed to address excess wrist movement during sedentary activities. However, there is not yet any consensus on which algorithms should be used. Also, algorithms developed in a population of healthy adults will not be accurate in an older population with reduced mobility, and the accuracy does not always hold up in 'real life' free-living settings. A recent study compared the accuracy of 9 wrist-specific predictive models against data collected at the hip using the ActiGraph device in free-living settings[235]. Large differences were noted for MVPA, light physical activity and sedentary behavior (correlations were low to medium), and physical activity estimates were all higher at the wrist. These findings emphasize the need to be cautious when interpreting studies that have used wrist devices and different processing methods. Another current challenge with machine learning approaches is the complexity of data processing and data storage requirements. At this stage of development, the amount of raw data processing is unrealistic when dealing with larger datasets in labs or clinical groups that are not equipped accordingly. The work we have presented in *Manuscript 5* demonstrates that data collected at the wrist and processed using the same cut points as at the waist overestimates physical activity and step counts and impacts the relationship with arterial stiffness. Our results were included in a recent meta-analysis evaluating the association between step counts and

arterial stiffness[236]. Interestingly, they observed a stronger association between steps and arterial stiffness in pedometer studies (pooled correlation estimate -0.23, 95% CI -0.34, -0.12) than accelerometer studies (0.12, 95% CI -0.21, -0.04), which may be attributed the different accelerometer wear locations (waist, arm, wrist). Therefore, until standardized machine learning/raw data processing methods are improved for the free-living assessment of physical activity and made accessible to researchers, it is probably advisable to continue with waist placement in order to accurately evaluate associations with clinical measures. However, these findings should not discourage physicians from engaging patients with wrist-worn devices as the emphasis should be on monitoring trends over time. Other accelerometer placement sites such as the chest (attached to a band or bra strap), have been shown to correlate well with activity recorded at the waist and could also be considered[237].

A recent qualitative study of an intradialytic pedaling program in the UK aimed to explore facilitators and barriers to initial and ongoing participation from the perspectives of exercising patients and dialysis unit staff[238]. They carried out focus groups before starting the intervention and followed up 6 months later with semi-structured individual interviews. The staff shared concerns about their already busy workload, as well as a lack of time and resources. Interestingly, patients worried about creating additional work for the staff but viewed the program as an opportunity to overcome exercise barriers and make positive use of the time spent on dialysis. Overall, staff and patients reported very positive experiences after engaging in the program. Functional improvements, better health outcomes, improved mood and a reduction in symptoms were reported by patients and staff as important motivators for continuing. Nevertheless, the added workload for staff remained a primary barrier. While we did not conduct a formal qualitative evaluation of our intervention, similar experiences were noted. Patients

responded positively to the intervention. Initially many continued with the pedaling exercise, but it became difficult once our research team was no longer present to help coordinate with the dialysis staff. We involved the hospital's volunteer program to assist as they were already helping to provide patient support in the unit (playing bingo, assisting patients with various tasks, etc.); however, volunteers were not consistently present, and high turn-over made training difficult. Unfortunately, the dialysis unit staff were not willing to run the program themselves. Our own experience and the findings from the qualitative work by Young and colleagues highlight the need for additional support within the unit. Other centres in Canada have demonstrated that these hurdles can be overcome, with patients and dialysis units enthusiastically committed to pedaling further: *"Throughout dialysis units across southern Alberta, dialysis patients are participating in their own Kidney March. Challenged to complete 100 kilometres of activity, patients pedal on specialized bikes that are pushed up to the dialysis chair. So far Jake, pictured above, has cycled 500 km en route to his goal of 800 km by September 7th. Being active while dialyzing is shown to clear more toxins from the blood and we applaud Jake and all our participants! In addition to getting several other benefits derived from leading a more active lifestyle, these participants are also raising funds for The Kidney Foundation of Canada.*[239]*"* The Southern Alberta Renal Program has organized one of the largest pedaling exercise programs for patients with dialysis and is available across 9 different sites[240]. Two kinesiologists are involved and travel between sites to help coordinate the program, providing guidance and support to patients and dialysis staff. Similar efforts should be made by other centres to evaluate how intradialytic pedaling exercise could be integrated in a sustainable manner into their dialysis unit. Future research studies will be needed to identify the optimal dose of pedaling exercise (intensity and time). Interestingly, a recent study evaluating a 14-week endurance-resistance training program showed that baseline physical activity status

influenced the level of responsiveness of physical function improvements to the intervention[241]. While this was not assessed directly in our trial due to a small sample size, we remarked that many of the patients were very inactive (IPAQ median 480 MET minutes/week), several of whom had an IPAQ of 0 (n=4) because they used a walker/wheelchair but were still able to pedal. The fact that they were not doing any physical activity may explain how a relatively short exercise intervention led to significant improvements in arterial health. Further supporting evidence from larger studies on health benefits and clinical outcomes will encourage the integration of intradialytic pedaling interventions into clinical guidelines and clinical practice.

Comparatively to a 1-year physician-delivered step count prescription intervention in the SMARTER trial, a 4 month intradialytic pedaling exercise intervention (PEDAL trial) led to a greater improvement in cfPWV (1 m/s vs. 0.2 m/s). The greater improvement in the PEDAL trial may be explained by the higher dose of physical activity; pedaling exercise for 48 minutes (group average) at low-moderate intensity 3 times per week translates to approximately 2,400 steps/day, which is double the average step count improvement observed in the SMARTER trial (1,200 steps/day). Pedaling exercise was also completed at a higher intensity than walking exercise, and volunteers motivated participants to reach the target range of 12-16 out of 20 points ("somewhat hard" to "hard") on the Borg Rating of Perceived Exertion Scale. This likely played a role as higher exercise intensity has been shown to lead to more significant improvements in arterial stiffness[24]. Taken together, a higher intensity and volume of exercise in the PEDAL trial likely contributed to the greater improvement in arterial stiffness than in the SMARTER trial.

The work presented in this thesis has focused on physical activity, but another important element to consider is sedentary behavior, which has emerged a distinct risk

factor[242]. Research into this area has expanded recently with the increased use of accelerometers which can objectively measure sedentary time, as well as identify and quantify bouts of sedentary time. Sedentary activities, such as screen-based leisure activities, desk-based work, and using motorised transportation consume a large portion of the day for the majority of individuals[243]. Canadians afflicted with at least one chronic disease are reported to spend more time in sedentary activity than individuals without chronic disease, and this amounts to approximately 9-10 hours/day[244]. Increased time in sedentary activities is associated with CVD risk and mortality, independently of physical activity levels[245,246]. A recent meta-analysis including data from over 1 million adults showed that meeting physical activity recommendations does not eliminate the elevated mortality risk associated with high sitting time (>8 hours/day)[242]. Only high levels of moderate physical activity (60-75 mins per day) was shown to eliminate risk. Among inactive and low active individuals, sitting time showed a graded association with mortality risk. In adults at risk of T2DM, interrupting sitting time with short bouts of light-moderate physical activity, such as walking, has been associated with attenuated postprandial glucose and insulin levels in adults who are overweight/obese and those with T2DM[247,248]. Our SMARTER intervention was successful in increasing pedometer-assessed step counts accumulated over the course of the day which led to improvements in cardiometabolic measures, but future efforts could also consider how we can reduce or help break up sedentary activities. As previously mentioned, this could be accomplished with reminders to move around from monitoring apps, or specific goals to disperse the number of steps throughout the day to help reduce long bouts of uninterrupted sitting. Trials will be needed to evaluate the effectiveness of this approach on cardiometabolic health outcomes. Higher sedentary time has been reported in individuals on hemodialysis[249]. A recent analysis of accelerometer-assessed sedentary

time linked with GPS locations among hemodialysis patients indicated that sedentary time at the hospital accounted for 18% of total sedentary time[250]. Therefore, an intradialytic pedaling exercise program provides an ideal means of replacing inactive sitting with light to moderate physical activity, and which may contribute to the health benefits of this type of intervention.

Other poor lifestyle behaviors, including lack of sleep, poor diet, and smoking tend to cluster with physical inactivity and high levels of sedentarism. These behaviors influence cardiometabolic health and are important targets for CVD prevention[251]. A bi-directional relationship has been noted between physical activity and sleep, where physical inactivity contributes to sleep disturbance, and poor sleep influences the motivation to be physically active[252]. Interestingly, increasing physical activity levels and physical fitness has been shown to improve sleep quality/duration[252]. Therefore, involvement in regular physical activity can help address sleep disturbance, thus improving cardiometabolic health, both directly and indirectly. Interventions combining dietary in addition to physical activity counseling have been shown to be more effective for weight loss than interventions with either diet or physical activity counseling alone[253]. Cardiometabolic improvements in response to dietary and physical activity changes are also greater; New Zealand's 'Green Prescription' program surveyed a representative sample of 1,488 participants and showed that those who increased their physical activity and changed their diet had a greater odds for weight loss, lower blood pressure, glucose and cholesterol levels, than participants who changed only one behavior[254]. Furthermore, while regular physical activity engagement improves CVD risk in both smokers and non-smokers, lifestyle interventions should encourage smoking cessation to maximize CVD risk reduction[255].

An important challenge to assessing the added benefit of physical activity monitoring in clinical practice is a lack of responsive indicators, particularly in patients with well-controlled risk factors. Blood pressure, glucose and cholesterol levels are well-established risk factors for arterial stiffness and subsequent CVD[33,102]. As such, their measurement is often used as a proxy for arterial health, and the diagnosis and management of cardiometabolic diseases has traditionally relied on these indirect measures[197]. However, this paradigm is shifting as technological advances have enabled the development of approaches such as applanation tonometry, which allows us to more directly assess the health of the arteries. As introduced previously, the degree of stiffness of the arteries reflects the cumulative impact of cardiovascular risk factors (e.g., blood pressure, glucose and cholesterol levels) and their interactions on the arteries over time, and thus provides a summative measure of arterial health[22]. Notably, cfPWV provides incremental value for CVD risk stratification, beyond traditional risk factors, including blood pressure[22]. The measurement of arterial stiffness is particularly relevant in a treated population. For example, the majority of SMARTER trial participants had well-controlled risk factors, but a wide range in arterial stiffness values was observed; despite adequate control of blood pressure, cholesterol and glucose levels, adults with T2DM had higher arterial stiffness. As demonstrated in *Manuscript 3*, the non-invasive measurement of cfPWV in our PEDAL trial allowed us to capture the cardiovascular benefit of intradialytic pedaling exercise in a hemodialysis population, which was not apparent when assessing blood pressure[25]. Additionally, the measurement of cfPWV in the context of acute exercise has improved our understanding of the cardiovascular response to a maximal exercise bout in patients with T2DM: increased central artery stiffness during exercise likely contributes to the exaggerated blood pressure response in participants with T2DM. As previously discussed, increased central arterial stiffness

has a number of clinical consequences, and an exaggerated arterial stiffness response to exercise (or even physical stress during daily activities) may contribute to the increased risk for cardiovascular events in these individuals. Therefore, similar to the 'cardiac stress test', the 'arterial stress test' may serve as a useful tool for cardiovascular risk stratification, and should be evaluated in future research. As we consider using arterial stiffness measurements for clinical applications going forward, there is a great need to ensure that standardized procedures are adopted. Our work in *Manuscript 6* provides evidence that different methods for assessment can lead to clinically relevant differences in the reported cfPWV. The development of less operator-dependent devices such as the XCEL system (partly cuff-based, as used in our PEDAL trial) or the Mobil-O-Graph (fully cuff-based) can reduce some of the measurement variability associated with cfPWV measurements, but it still remains important that a standardized method is followed. While the measurement of arterial stiffness has been more strongly supported by clinical guidelines in Europe[154], we have not yet seen the widespread uptake of arterial stiffness measurement in clinical practice. While on a statistical level, arterial stiffness has been shown to predict CVD risk independently of blood pressure and other traditional risk factors, it is more challenging to assess the level of risk in clinical practice when arterial stiffness measurements are confounded by blood pressure. To address this, efforts are being made to identify blood pressure-independent measures of arterial stiffness, such as the aortic stiffness β_0. As we have introduced in *Manuscript 4*, aortic stiffness β_0 adjusts cfPWV for the diastolic blood pressure at the time of measurement. However, reference values will need to be established before we can consider using this metric in clinical decision making.

8.5 Limitations

I would like to acknowledge the following limitations of the work presented in this thesis.

(1) Aside from the PEDAL trial, the findings presented were derived from cross-sectional observational studies. For this reason, we cannot establish causation or draw conclusions about the direction of the associations observed.

(2) In several studies (*Manuscripts 1, 2, 4, 5 and 6)*, I carried out secondary analyses using existing data. The original studies were not specifically designed to address my research questions herein, which has introduced a number of limitations that were summarized in each of the manuscripts. However, it is worth mentioning that I was involved in the primary data collection for each of the studies and was very familiar with all the methods and data collection processes that were used. Therefore, I was able to ensure all of the data was were used appropriately, thus preventing common pitfalls encountered by researchers when conducting secondary analyses on primary data they are not as familiar with. Similarly, all measurements were completed at the Vascular Health Unit following the same standardized protocol. Nevertheless, these limitations should still be considered in the work we have presented and addressed in future work.

(3) The generalizability of our findings should also be considered. The qualitative follow-up and trajectory analysis of the SMARTER trial are specific to older sedentary to low active adults with T2DM and/or hypertension. Individuals with other chronic diseases would likely also benefit from a physician-delivered step count prescription strategy (e.g., CKD, heart failure, cancer). However, these populations may identify different facilitators/barriers associated with the

strategy, and these differences may influence the trajectories of step count change. Furthermore, the PEDAL trial was conducted in a selected group of hemodialysis patients without overt cardiac disease. While it is possible that lower intensity pedaling exercise may be tolerated in these individuals, our results are not generalizable to patients with more advanced CVD who were unable to participate in the trial.

(4) Missing data was encountered in a number of the studies (*Manuscripts 2, 3, 4, and 5*). In SMARTER, few participants were 100% compliant in recording their step counts daily for a 1-year period. To control for this limitation, we only considered 30-day periods where more than 50% of step count entries were present. This led to missing data at certain time points; however, GBTM is a method that can accommodate missing data points as it uses maximum likelihood estimation. We evaluated other thresholds for missing data in sensitivity analyses (25% and 75%) and the results were unchanged. Furthermore, we did not have a year of step count data in all participants but established that few participants were reclassified when we carried out the analysis using only the first 6 months of data in all participants. We also encountered missing arterial stiffness data in SMARTER participants after the exercise stress test. The missingness was mainly a result of recordings not meeting our quality control criteria. When PWV values are high, the denominator (time) becomes small, and small differences in pulse transit time exaggerate the variation beyond the acceptable threshold. Therefore, these data were considered to be missing at random as the probability of the missing data was influenced by the observed value. Technical difficulties also led to missing data, but this occurred at completely at random. We decided to exclude participants with missing data at

the 3-minute time point but acknowledge that the presence of missing data introduces a risk for bias.

(5) We opted to carry out per-protocol analyses rather than intention-to-treat analyses in the PEDAL trial (*Manuscript 3*) and would like to acknowledge the limitations of this approach. The analysis of only completers can introduce bias and in theory, violates the principle of randomization; when participants are excluded (from one or both groups), the remaining participants may no longer be balanced. In PEDAL, the baseline characteristics of all participants (completers and non-completers) were similar to those who completed the intervention. In both cases, the groups were comparable in terms of arterial stiffness and known confounders. However, we acknowledge that we cannot ensure that the groups included in our analysis are balanced in terms of unmeasured confounders. The reasons for non-completion of the trial included a drop out from the control arm, kidney transplants, unrelated medical conditions or death (post-surgical complication) which prevented us from obtaining measurements from these participants at the end of the trial. Since the publication of this manuscript, we carried out an additional analysis where the last value (baseline value) was carried forward for participants who dropped out of the exercise intervention (N=6). Despite this conservative approach, a similar between-group difference was noted in the response of cfPWV (0.94 m/s [0.14, 1.75]). However, we were not able to include participants (N=5) who dropped out after randomization but before starting the exercise intervention as they did not have a baseline arterial stiffness value.

(6) The possibility of selection bias should be noted. Selection bias can influence the observed association if the sample included in the study is not representative of the distribution of the exposure and outcome in the target population. In both the

SMARTER and PEDAL trials, participants who agreed to participate in the exercise interventions may be healthier and more motivated. Similarly, physicians who were willing to take part in the SMARTER trial may not be representative of the wider population of physicians; and thus our qualitative findings in this group of more motivated physicians may not reflect the views of all physicians. However, efforts were made to interview a sample of SMARTER participants that would be representative of the larger group of participants (including participants who both increased and decreased their steps) and physicians involved in the trial (low and high recruitment numbers). Similarly, for our other studies where analyses were conducted in a selected sample of participants, we compared characteristics of participants who were included and those who were excluded (*Manuscripts 2, 4 and 6*). Additionally, loss to follow-up is another source of selection bias to consider *(Manuscript 2, 3).*

8.6 Future Directions

As we move towards the widespread implementation of a physician-delivered step count or physical activity prescriptions, possible adaptations may need to be considered to optimize the incorporation into clinical care and uptake by all physicians. For example, the strategy could be combined with adjunctive counseling from other members of the health care team. The idea of integrating the strategy into the clinic with the help of other health professionals such as nurses, dieticians, diabetes educators was very much supported by the interviewed physicians in our study. Additionally, whether support between-visits from a virtual coach, peers or both, could amplify the effects of the intervention will be investigated in future studies by the SMARTER investigators. In light of the independent health risks associated with excessive sedentary time, future studies

with accelerometer data collected over time should evaluate trajectories of sedentary time in addition to step counts and other physical activity metrics. Our analyses were underpowered to evaluate associations of trajectory shape with clinical measures, but this should be investigated in future studies.

The findings from our pilot randomized controlled trial evaluating the arterial health impact of intradialytic pedaling will need to be confirmed in future investigations. Multicenter studies could be considered to increase the number of participants and overcome the higher drop-out rate because of transplants and other health changes that influenced participation in the exercise program. Longer durations of exercise should also be evaluated to assess the longer-term effects on cardiovascular measures but also to assess exercise compliance over a longer period (6 months-1 year).

Our findings evaluating the arterial stiffness response to acute maximal exercise in individuals with and without T2DM, indicated that arterial stiffness likely influences the elevated blood pressure response in individuals with T2DM. The bi-directional relationship between blood pressure and arterial stiffness should be examined further in the context of acute exercise. While we adjusted for blood pressure and incorporated a blood pressure-independent measure, future studies could incorporate simultaneous ultrasound measurements in order to generate pressure-area curves and examine changes in arterial stiffness (tangent slope) with changes in blood pressure. Future studies designed to explore the clinical potential of the 'arterial stress test' are also needed, and should examine the arterial stiffness response to exercise in lower-risk individuals with T2DM with normal arterial stiffness values at rest compared with healthy controls.

As new wrist-specific algorithms are developed for the quantification of steps and physical activity, they will need to be assessed carefully. When comparing different

algorithms, future researchers should also consider the impact of any differences between methods on associations with relevant clinical outcomes. Our methodological assessment of different arterial stiffness methods indicated important differences in the reported cfPWV value. The next step should ideally involve the acquisition of invasive measures of arterial stiffness and clinical outcomes to evaluate the most accurate and clinically relevant method for reporting of arterial stiffness indices.

8.7 Concluding Remarks

With an increasing prevalence of chronic disease, there is a pressing need for effective and realistic strategies to help physicians support and engage their patients to achieve the health benefits of higher physical activity levels. The promotion of physical activity in the clinical setting is a promising approach. Using qualitative and quantitative methods, we have delineated factors that contributed to effectiveness of a step count prescription and monitoring strategy, and identified potential modifications for future implementation. Overall, our findings support the adoption of a prescription strategy across a wide range of individuals with T2DM and/or hypertension with varied baseline activity levels. The importance of increasing daily step counts has been highlighted by recent studies that demonstrate mortality benefits associated with even small increases in steps[64,65]. Additional support from other members of the health care team may allow physicians to feel more supported and motivated to continue engaging in the strategy over time and may amplify the impact of the intervention.

Improved metrics for evaluating cardiovascular health in individuals with well-controlled risk factors are also needed, whether to examine the impact of an exercise program or evaluate CVD risk in a clinical setting. This thesis work supports the added value offered by the non-invasive assessment of arterial stiffness. We demonstrated that

an intradialytic pedaling exercise is a safe and effective modality for engaging individuals with CKD in regular physical activity, and importantly, has a beneficial effect on arterial stiffness. The reversibility of the effects after discontinuation emphasizes the need for maintenance of regular physical activity in this population. Measurements of arterial stiffness in the context of acute maximal exercise (the 'arterial stress test') provided us with a useful model for examining the ability of the arteries to respond to increased demands. Individuals with T2DM were shown to exhibit an altered arterial stiffness response to acute maximal exercise compared to individuals without T2DM independently of blood pressure elevation. These findings add another dimension to our understanding of vascular impairment in the context of T2DM.

Finally, this thesis provides researchers with concrete evidence regarding the impact of accelerometer placement on physical activity levels and associations with a relevant health outcome, as well as the impact of different approaches for collecting cfPWV values on the reported value. These findings highlight the necessity for standardized research protocols in this area.

Taken together, these novel contributions will a) guide future research evaluating physical activity and cardiovascular health using modern methods such as accelerometry and applanation tonometry, and b) facilitate building refined and sustainable physical activity strategies to address the high levels of inactivity and elevated CVD risk in individuals with hypertension, T2DM and CKD.

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APPENDIX

Appendix A – Presentations and awards at scientific conferences related to thesis work

Published Abstracts (7)

Cooke AB, Kuate Defo A, Chan D, Rahme E, Daskalopoulou SS, Dasgupta K. A Trajectory Analysis of Daily Step Counts During a Physician-Delivered Intervention. *Canadian Journal of Diabetes*. 2019 Oct; 43(7), S39.

Cooke AB, Dasgupta K, Daskalopoulou SS. Altered Vessel Hemodynamics After Acute Maximal Exercise in Adults with Type 2 Diabetes. *Artery Research 2018.*

Cooke AB, Daskalopoulou SS, Dasgupta K. The Impact of Accelerometer Wear Location on the Relationship between Step Counts and Arterial Heath in Free-Living Adults. *Artery Research* 2017.

Cooke AB, Daskalopoulou SS, Dasgupta K. Seasonal Variations in Step Counts, Physical Activity Intensity and Sedentary Behavior in Type 2 Diabetes and Hypertension. *Canadian Journal of Diabetes*. 2016 Oct; 40(5), S55.

Cooke AB, Ta V, Gomez YH, Iqbal S, Daskalopoulou SS. The Arterial Health Impact of Intradialytic Pedaling Exercise in a Hemodialysis Population. *Artery Research.* 2016 Dec; 16, p 99-100.

Cooke AB, Mutter AF, Saleh O, Gomez YH, Daskalopoulou SS. A systematic review on the effect of acute aerobic exercise on arterial stiffness reveals a differential effect on upper and lower limb arterial segments. *Artery Research.* 2016 Dec; 16, p95.

Cooke AB, Daskalopoulou SS, Dasgupta K. Step Counts and Sedentary Time in Type 2 Diabetes and Hypertension: Seasonal Variations. *Obesity Reviews* 2015;17 (Suppl 2), 84-85.

Oral Presentations (6)

Cooke AB, Dasgupta K, Daskalopoulou SS. From Rest to Stressed: Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Hemodynamics. Hypertension Canada, September 25-28, 2019. Edmonton, Alberta.

Cooke AB, Dasgupta K, Daskalopoulou SS. Altered Vessel Hemodynamics After Acute Maximal Exercise in Adults with Type 2 Diabetes. North American Artery 8th Annual Meeting, June 15-16, 2018. Chicago, Illinois.

Cooke AB, Daskalopoulou SS, Dasgupta K. Wrist versus Waist: The Impact of Accelerometer Wear Location on the Relationship between Step Counts and Arterial Stiffness in Adults Treated for Hypertension and Diabetes. Canadian Hypertension Congress, October 12-15, 2017, Toronto, ON.

Awarded $900 Trainee Travel Award from Hypertension Canada.

Cooke AB, Daskalopoulou SS, Dasgupta K. The Impact of Accelerometer Wear Location on Physical Activity Estimates and the Relationship with Arterial Health in Adults Treated for Hypertension and Diabetes. 5th Canadian Obesity Summit, April 25-29, 2017, Banff, AB.

Dasgupta K, **Cooke AB**, Rosenberg E, Joseph L, Daskalopoulou SS. Carotid Femoral Pulse Wave Velocity is Responsive to Step Counts in Adults Treated for Hypertension and Diabetes. Canadian Hypertension Congress, October 19-21, 2016, Montreal, QC. (*presented by Cooke AB).

Cooke AB, Ta V, Gomez YH, Iqbal S, Daskalopoulou SS. The impact of intradialytic pedaling exercise on arterial stiffness in a hemodialysis population. North American Artery 6th Annual Meeting, September 9-10, 2015, Chicago, Illinois.

Workshops (3)

McGill Annual Refresher Course for Family Physicians. Hotel Bonaventure Montreal, QC, November 27, 2017. Delivered session with Dasgupta K and Chan D.

Primary Care Provider's Symposium at Diabetes Canada 20th Professional Conference, Step Monitoring to improve ARTERial health: trial results and step count prescriptions. Edmonton, AB, November 4, 2017. Delivered session with Dasgupta K and Chan D.

Pragmatic Trials Workshop at Journée scientifique annuelle du Réseau-1. McGill University, Montreal, QC, June 16, 2017. Delivered session with Rosenberg E and Chan D.

Poster Presentations (16)

Cooke AB, Kuate Defo A, Chan D, Rahme E, Daskalopoulou SS, Dasgupta K. A Trajectory Analysis of Daily Step Counts During a Physician-Delivered Intervention. 21st Annual Diabetes Canada/ Canadian Society of Endocrinology and Metabolism Professional Conference, October 2-5, 2019. Winnipeg, Manitoba.

Cooke AB, Kuate Defo A, Phan K, Retamal J, Daskalopoulou SS. Methodological Considerations for the Measurement of Arterial Stiffness using Applanation Tonometry. North American Artery 9th Annual Meeting, May 17-18, 2019, Iowa City, Iowa.

Cooke AB, Dasgupta K, Daskalopoulou SS. From Rest to Stressed: Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics. CIHR Canadian Student Health Research Forum, June 10-15, 2019, Winnipeg, Alberta.
Nominated by McGill to attend as being in the top 5% of PhD students from universities across Canada. Received Gairdner Award and Gold Poster Presentation Award (given to the top 5 poster presentations out of 130 presentations)

Cooke AB, Dasgupta K, Daskalopoulou SS. From Rest to Stressed: Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics. McGill Cardiovascular Research Day, May 2, 2018. Montreal, QC.

Cooke AB, Dasgupta K, Daskalopoulou SS. From Rest to Stressed: Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics. McGill Department of Medicine Research Symposium, May 10, 2018. Montreal, QC.

Cooke AB, Dasgupta K, Daskalopoulou SS. From Rest to Stressed: Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics. Experimental Biology 2018. April 21-25, 2018. San Diego, CA.

Cooke AB, Dasgupta K, Daskalopoulou SS. From Rest to Stressed: Adults with Type 2 Diabetes Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics. Centre for Health Outcomes Research Day, February 20, 2018. Montreal, QC.

Cooke AB, Daskalopoulou SS, Dasgupta K. Relation entre le nombre de pas et la rigidité artérielle chez des adultes diabétiques et hypertendus: impact de l'emplacement de l'accéléromètre. La Société québécoise d'hypertension artérielle (SQHA) 26ième Réunion scientifique annuelle, January 24-25, 2018, Quebec City, QC

Cooke AB, Daskalopoulou SS, Dasgupta K. The Impact of Accelerometer Wear Location on the Relationship between Step Counts and Arterial Heath in Free-Living Adults. North American Artery 7th Annual Meeting, May 19-20, 2017, Chicago, Illinois.

Cooke AB, Daskalopoulou SS, Dasgupta K. The Impact of Accelerometer Wear Location on Physical Activity Estimates and the Relationship with Arterial Health in Adults Treated for Hypertension and Diabetes. 5th Canadian Obesity Summit, April 25-29, 2017, Banff, AB.

Cooke AB, Daskalopoulou SS, Dasgupta K. Seasonal Variations in Step Counts, Physical Activity Intensity and Sedentary Behavior in Type 2 Diabetes and Hypertension. 19th Annual CDA/CSEM Professional Conference and Annual Meetings October 26-29, 2016, Ottawa, ON.

Cooke AB, Ta V, Gomez YH, Iqbal S, Daskalopoulou SS. The Arterial Health Impact of Intradialytic Pedaling Exercise in a Hemodialysis Population. Canadian Hypertension Congress, October 19-21, 2016, Montreal, QC.
Received Canadian Hypertension Congress Outstanding Poster Presentation Award

Dasgupta K, **Cooke AB,** Rosenberg E, Joseph L, Daskalopoulou SS. Relationship between step counts and carotid femoral pulse wave velocity in adults treated for hypertension and diabetes. North American Artery 6th Annual Meeting, September 9-10, 2015, Chicago, Illinois.

Cooke AB, Mutter AF, Saleh O, Gomez YH, Daskalopoulou SS. A systematic review on the effect of acute aerobic exercise on arterial stiffness reveals a differential effect on

upper and lower limb arterial segments. North American Artery 6th Annual Meeting, September 9-10, 2015, Chicago, Illinois.

Cooke AB, Daskalopoulou SS, Dasgupta K. Step Counts and Sedentary Time in Type 2 Diabetes and Hypertension: Seasonal Variations. McGill Cardiovascular Research Day. Montreal, QC, May 25, 2016.

Cooke AB, Daskalopoulou SS, Dasgupta K. Step Counts and Sedentary Time in Type 2 Diabetes and Hypertension: Seasonal Variations. International Congress on Obesity, May 1-4, 2016, Vancouver, BC.

Appendix B – SMARTER Step Count Prescription Template

SMARTER

FOR MORE INFORMATION ABOUT THE SMARTER TRIAL, please see *Diabetes, Obesity, and Metabolism*. 2017 May;19(5):695-704 PMID: 28074635

Possible step count increments by clinic visits to aim for increase of 3,000 steps per day above baseline in approximately 1 year (for Physician's reference).

Steps per day at *baseline*	Clinic Visit 1 (after baseline step count determined – 0 months)	Clinic Visit 2 (3 months)	Clinic Visit 3 (6 months)	Clinic Visit 4 (9 months)
< 5 000	+ 500	+ 750	+ 750	+ 1 000
5000 – 7 499	+ 750	+ 1 000	+ 1 250	
≥ 7 500	+ 1 000 / +2 000	+ 1 000		

Today's Date: _____

Patient name: _____

Baseline Step Count: _____
Which visit is this? _____

Steps start date: _____
Recommended Step Count: _____

SMARTER

Step count prescription

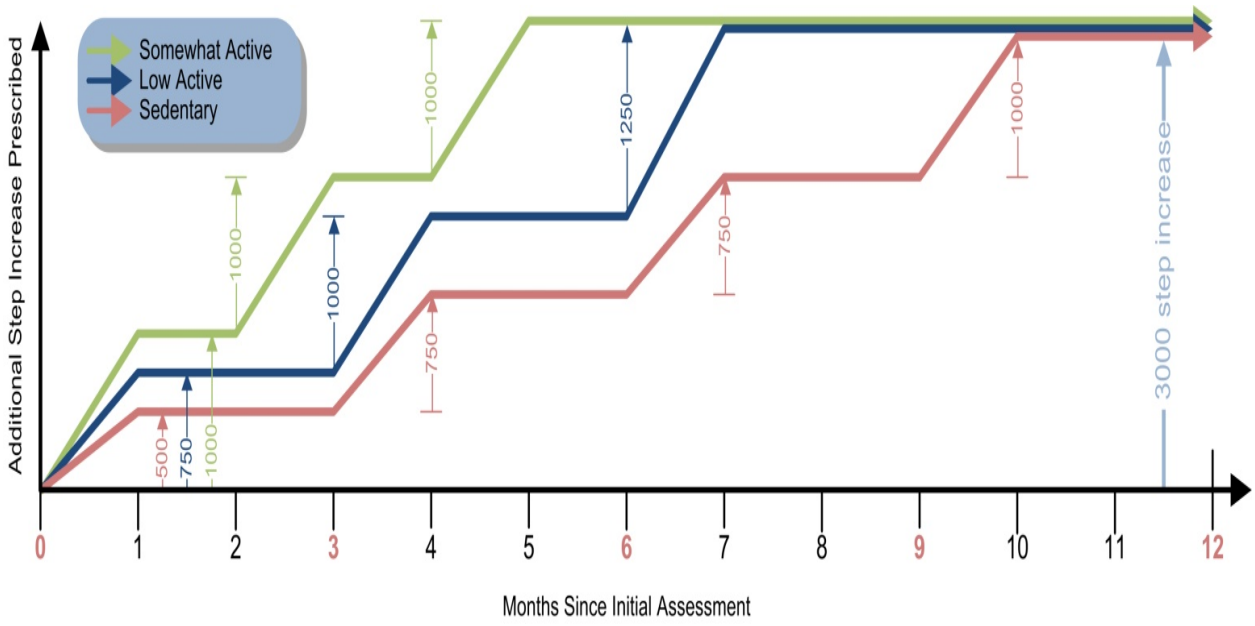
Today's Date: _____

Patient name: _____

Please try to complete *at least* _____ steps per day until your next clinic visit.
Please record you step counts in your log sheets at the end of each day.
Please bring your log sheets to the next clinic visit which will be in about three months.

Physician's Name _____ Physician's Signature _____

Appendix C - SMARTER step count prescription framework



SMARTER step count prescription framework by baseline activity category. Clinic visits occurred at 0, 3, 6, 9 and 12 months. Prescriptions were given at months 0, 3, 6, and 9. The goal was for all participants to achieve a net increase of at least 3,000 steps/day from baseline.

Appendix D: SMARTER Trial Semi-Structured Interview Guides

Semi-Structured Interview Guide for SMARTER Collaborating Physicians

1. Tell me about your experience with your patients in the intervention arm of the step count study. Try to think about a particular patient and talk through your experience over the year.

If the case described is a positive one, ask whether this case is typical or whether there were less successful ones. If the case is a negative one, ask whether there were more successful ones. Then ask for a description of a second case focusing on what made it different from the first one.

Probes:

What were some of the issues/challenges patients encountered?

Was the strategy easy for your patients to understand?

If not, what did you do?

Did they put the pedometer on every day?

If not, what did you do?

Did they fill in the log book?

If not, what did you do?

Were they able to increase steps according to the suggested rate?

If not, what did you do?

Do you feel the step count prescription strategy had a more beneficial impact on your patient's physical activity habits compared to your usual advice regarding exercise recommendations?

Did you notice a difference in your patient's motivation to be more physically active once you started the intervention with them?

Did you notice that their motivation changed throughout the intervention?

Did you notice any changes in their motivation after the intervention ended?

What was the major barrier for implementation of the strategy?

2. Tell me about your experience implementing the step count prescription strategy in your clinic.

Probes:

Have you found that using the step count prescription strategy impacted the amount of time you spent with patients?

Did you change the frequency of your visits with patients?

Did the strategy require any change in the work of others in the clinic?

If yes, explain.

How did the SMARTER coordinator impact your use of the strategy?

3. Tell me about your practice with sedentary patients since the study and what you might do in the future.

Probes:

Did you continue to set step count goals and request feedback from SMARTER trial patients in your clinic after they completed the study? Did you set step count goals with control arm participants in your clinic after they were given a pedometer?

Why, why not.

Have control arm subjects started to report their step counts to you since receiving a pedometer?

Have you used any elements of the strategy with other patients?

If yes, how did you choose the patients, what elements did you use?

Probe: prescription pad, patient step logs, pedometers

Would you feel comfortable suggesting that your patients purchase a pedometer? Do you think that you know enough information about pedometers if you were to propose this to your patients?

If no, why not.

Do you think patients would have different response to the prescription strategy if a nurse were to be the one speaking with the patient and providing the prescription?

In your practice are you able to access such a nurse?

Semi-Structured Interview Guide for SMARTER Active Arm Participants

You got a pedometer and a prescription from your doctor to walk a certain number of steps every day. We'll call this the program.

1. **Can you describe the program and what it was like for you?**

Probes:

What did you like or dislike about the program?

What were challenges some of the challenges you faced?

Did you have any difficulty understanding what you were supposed to do?

If yes, what did you do?

Did you put the pedometer on every day?

If yes, why?

Was it because your doctor gave you one?

How did the pedometer help you to be active?

If no, what made it hard to do?

Did your pedometer fall off or not record all your steps?

Has your pedometer run out of batteries? Did you replace them?

Has your pedometer broken?

Are you using another step tracking device?

Did you use the log book?

What did you do with your doctor's prescription?

What did you do to incorporate the program into your daily life?

Were you able to increase your number of steps the way your doctor suggested?

If not, what did you do?

Did you notice a difference in your motivation to be more physically active once you started the program?

Is walking easier for you to do than other physical activity?

If yes, why?

Did walking more have any bad effects on you?

If yes, tell me about them.

How was your activity affected by the weather?

Did the program have an effect on your health?

Ask for details.

2. **What helped you to follow the program?**

Probes:

Did others encourage you to walk? Who were they?

Has your pedometer use influenced people around you (family members, friends, coworkers etc.) to change their daily exercise habits?

3. **Tell me about your physical activity since the program ended.**

Probes:

Do you feel you are walking more, less or about the same?

Have you continued to use a pedometer since the research program ended?

If yes:

Have you set goals for yourself? Do you record the number of steps each day?

Have you continued to discuss step count goals with your doctor?

If no:

What were the reasons you stopped using your pedometer?

Have you maintained your walking habits without needing to use the pedometer?

Are you using another fitness tracking device?

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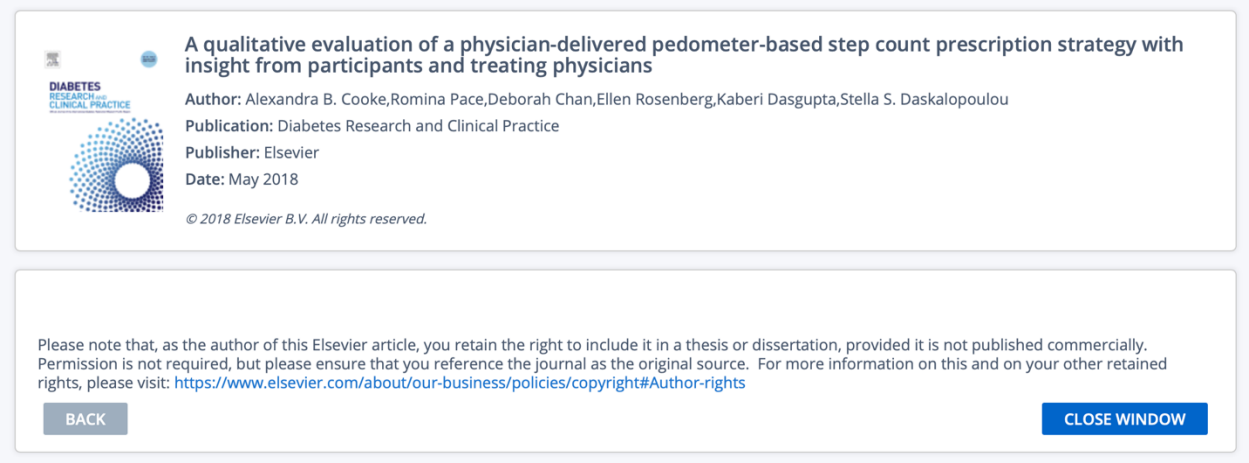

A qualitative evaluation of a physician-delivered pedometer-based step count prescription strategy with insight from participants and treating physicians

Author: Alexandra B. Cooke,Romina Pace,Deborah Chan,Ellen Rosenberg,Kaberi Dasgupta,Stella S. Daskalopoulou

Publication: Diabetes Research and Clinical Practice

Publisher: Elsevier

Date: May 2018

Appendix F – Copyright permissions for Manuscript 2

A trajectory analysis of daily step counts during a physician-delivered intervention

Author: Alexandra B. Cooke,Elham Rahme,Alvin Kuate Defo,Deborah Chan,Stella S. Daskalopoulou,Kaberi Dasgupta

Publication: Journal of Science and Medicine in Sport

Publisher: Elsevier

Date: Available online 18 April 2020

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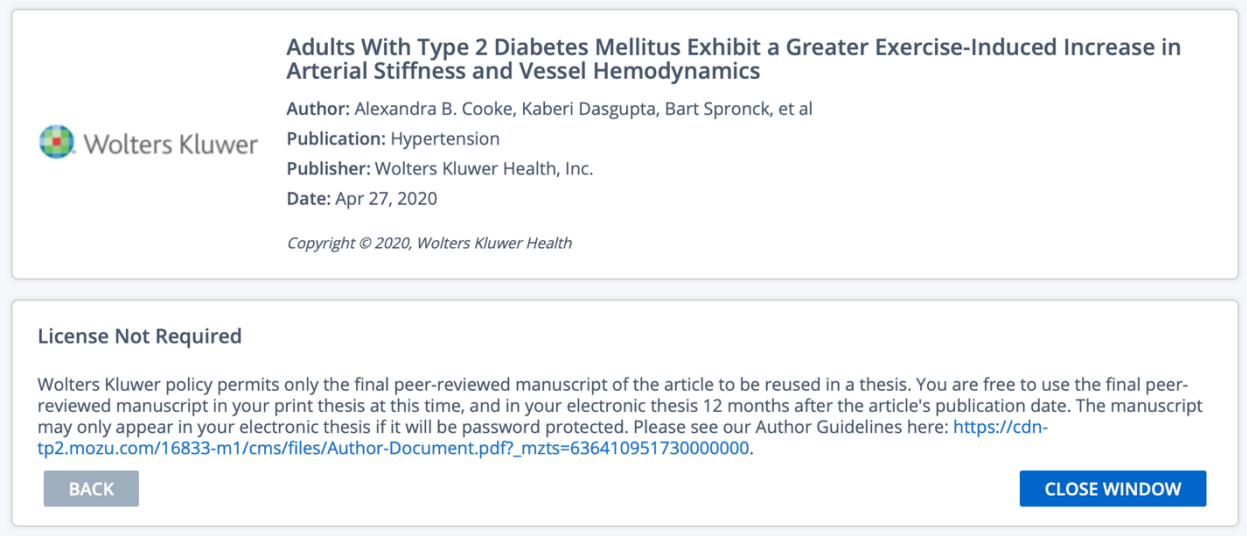

Adults With Type 2 Diabetes Mellitus Exhibit a Greater Exercise-Induced Increase in Arterial Stiffness and Vessel Hemodynamics

Wolters Kluwer

Author: Alexandra B. Cooke, Kaberi Dasgupta, Bart Spronck, et al

Publication: Hypertension

Publisher: Wolters Kluwer Health, Inc.

Date: Apr 27, 2020

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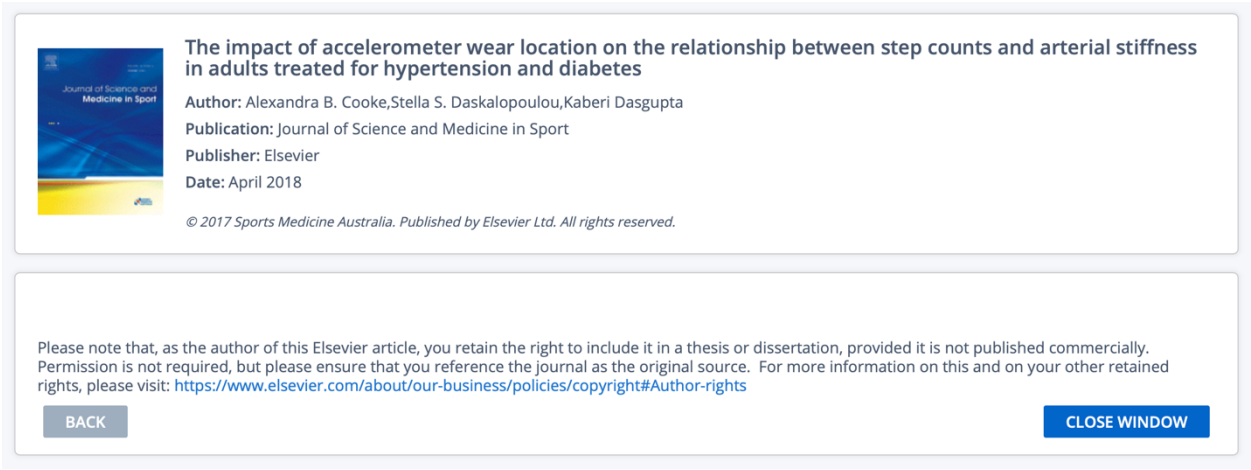

The impact of accelerometer wear location on the relationship between step counts and arterial stiffness in adults treated for hypertension and diabetes

Author: Alexandra B. Cooke,Stella S. Daskalopoulou,Kaberi Dasgupta

Publication: Journal of Science and Medicine in Sport

Publisher: Elsevier

Date: April 2018