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REVIEW

Unmet Needs and Opportunities for Australian Innovation and Clinical Research to Improve Quality of Life and Outcomes in Patients With Peripheral Artery Disease

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Peripheral arterial disease (PAD) is characterised by atherosclerotic stenosis or occlusion of arteries that leads to reduced blood flow to the limbs. PAD is associated with a very high rate of cardiovascular morbidity and mortality making the health and economic burden of PAD substantial. Despite high-quality evidence and international guidelines recommending conservative medical management of risk factors, and exercise and lifestyle interventions, surgical revascularisation (open or endovascular) remains the main treatment for PAD. Alarmingly, up to one-third of patients do not receive best medical therapy after revascularisation surgery despite evidence supporting this treatment reduces cardiovascular events.

Due to the considerable health burden that PAD presents, this manuscript aims to identify gaps in care and clinical research in PAD across Australia and proposes potential collaborative solutions. In Australia, there is significant disparity in care between rural/regional and metropolitan communities. These gaps are exacerbated by inequitable access to services across Australia, particularly for First Nation Australians, culturally and linguistically diverse groups and those living in regional and remote areas. This review identifies unmet needs for patients with PAD that are multifaceted, spanning from improved understanding of disease mechanisms, diagnostic tools for risk stratification and personalised therapy, to a paucity of medical and rehabilitation therapies for symptoms or prevention of cardiovascular complications. Furthermore, there are opportunities for national and international registries to optimise clinical trial quality and outcomes. Strategies should be applied to improve implementation of optimal medical therapy in PAD which will improve quality of life, reduce health care costs, and prevent secondary complications, limb loss, and mortality across Australia's diverse population.

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The Burden of PAD

Atherosclerotic peripheral artery disease (PAD) is estimated to affect >230 million people worldwide [1,2] and is a strong predictor of cardiovascular (CV) morbidity and all-cause mortality [3]. Australian patients with PAD experience major adverse CV events (MACEs) at a rate of 7%–11% per year and have a 5-year all-cause mortality rate of 22% [4]. In addition to reduced physical health, patients with PAD also present with poor mental health including depression, with the prevalence of depressive symptoms ranging between 3%–48% across 28 studies in a 2017 systematic review [5]. Yet, there is a dearth of research on the prevalence of depression and other mental health conditions in patients with PAD in Australia. In 2017–2018, Australia saw over 33,100 PAD-related hospitalisations, leading to 1,845 deaths [6] and >8,000 amputations [7], with rural communities facing a three-fold higher risk compared to metropolitan populations. Remarkably, Australia has the highest rate of lower limb amputation among high-income countries reported in a previous systematic review [8]. This could be due to the high prevalence of diabetes, with currently 5.6% of the population or one in 20 Australians have diagnosed diabetes [9]. There are currently more than 4,400 amputations every year in Australia as a result of diabetes, which is the second highest rate in the developed world [8]. Furthermore, in Australia the rate of non-fatal burden due to lower limb amputations as a result of diabetes complications is three-fold higher for males when compared to females; highest among people living in the Northern Territory and remote areas; higher in groups who experience socioeconomic disadvantage when compared to those who do not, and higher in First Nation Australians, compared to non-First Nation Australians [10]. Similarly for PAD, outcomes are worst in women and First Nations Australians, who have a three-fold higher risk of developing PAD [11] when compared to men and non-First Nations Australians. The economic impact of PAD is therefore immense and consists of both direct (medical and surgical intervention, and rehabilitation), and indirect (related to impaired ability of patients to partake in the workforce) measures, with direct costs of hospitalisation in Australia being $347 million in 2019 [12]. This economic burden is predicted to increase with our ageing population and increasing incidence of diabetes.

Identified Gaps and Potential Solutions to Improve Outcomes and Quality of Life in PAD

This review reflects the diverse expertise and knowledge of the Australian Cardiovascular Alliance (ACvA) PAD Working Group and aims to identify priority gaps and opportunities across the strategic ACvA Flagships for clinicians and researchers across Australia to address through future research (Table 1). The flagships include Disease Mechanisms, Drug Discovery and Translation, Biomedical Engineering, Precision Medicine, Clinical Trials, Big Data, and Implementation and Policy. We have also outlined gaps identified in the use and implementation of exercise therapy, which is considered first-line therapy for patients with PAD. The formation of the ACvA PAD Working Group has allowed for a fully integrated national discussion between clinicians, consumers, researchers, health economists and industry on gaps in PAD care. In addition, we highlight how Australian researchers are contributing internationally to the management of PAD with the view to establishing further collaborations that will assist us with enhancing the care of the diverse Australian population suffering with PAD.

Guidelines Treatment Gaps

Current guidelines address various aspects of PAD management including diagnosis, risk management and treatment [13,14]. However, a minimum set of standardised clinical quality indicators and outcomes are needed for PAD that can be monitored by health and research leaders via national dashboards to inform research and implementation priorities. We present the initial steps towards this by the ACvA PAD Working Group, including the recently established National CV Health Leader Research Forum [15] with all State and Commonwealth Health Departments represented.

While surgery and endovascular revascularisation is the mainstay of intervention for severe symptomatic PAD, these are costly (~AUD$12,552/endovascular and ~AUD$40,134/open intervention) [16] and associated with complications and poor durability [17]. While revascularisation is vital in patients with limb threatening ischaemia, the place of this treatment in the management of intermittent claudication and other PAD presentations without limb threatening ischaemia is controversial. While an Australian study by Golledge et al. [17] was limited to patients with intermittent claudication, and adjusted for confounding factors, remarkably, a five-fold increase in the rate of major amputation was still apparent in people undergoing revascularisation [16,17]. Furthermore, a recent systematic review highlighted the limited benefits of endovascular revascularisation compared with exercise therapy for treating PAD-related walking impairment [18]. Despite this, over 10,000 endovascular and surgical revascularisation procedures are performed annually in Australia and New Zealand [19]. Furthermore, one-third of patients do not receive optimal medical therapy following infra-inguinal peripheral arterial

Table 1 Gaps and potential solutions across the pipeline.

Key priority area	Summary of unmet needs	Summary of potential solutions
Disease Mechanisms	• Understanding of PAD mechanisms • Understanding mechanisms mediating microvascular dysfunction and how it may differ between genders • Understanding the impact of age/gender on atherosclerosis and pathogenesis of PAD in preclinical models	• Further study on hind limb ischaemia in animal experiments in animals of both sex
Drug Discovery and Translation	• Therapies to reduce the incidence of ulceration and gangrene • Poor uptake and collaboration across national biobanks • Poor pharmacological options directly targeting underlying PAD mechanisms to improve function and QoL leading to increased incidence of surgical interventions	• Drug therapies to enhance tissue perfusion and angiogenesis • Improving access to, and the number of collaborative biobanks nationally • Improved pharmacological options directly targeting to improve function and QoL and reduce the need for surgical interventions • Clinical trials into repurposing drugs
Biomedical Engineering	• Detailed understanding of the effect of PAD on the individual patient • Addressing calcified atherosclerosis that resists intervention with balloons and stents alone	• Intravascular and non-invasive imaging • Real-time tissue diffusion devices • Surgical interventions such as stents and scaffolds, atherectomy devices, lithotripsy specifically developed for PAD
Precision Medicine	• Understanding effects of combination surgical plus exercise or pharmaceutical plus exercise therapy, or a combination of the three	• National and international clinical trials comparing the three medical management strategies
Exercise Management	• Understanding the mechanisms of benefit for exercise therapy • Clear formulation of Level A evidence for optimal exercise prescriptions • Research on exercise interventions for people with more severe disease and those with prosthetic devices • Holistic lifestyle intervention delivery strategies using technology • Understanding of why access to exercise programs is limited and under-funded in Australia • Understanding which exercise prescription is most beneficial across disease severity	• Establishment of human tissue biobanks nationally and internationally storing specimens from both pre and post exercise • Development of new exercise and physical interventions to target patients who are unable or are resistant to exercise • Exploring the use of technology to deliver advice on exercise, nutrition, reducing sitting time, and safe drug and alcohol use • Efficacy and implementation trials to help understand why access to exercise programs is limited and which prescriptions would be most beneficial across stages of disease
Clinical Trials	• Clear clinical end points relative to PAD used nationally • Uniform data collection for fitness, walking and functional outcomes in PAD	• Large clinical trials including clinical end points relative to PAD • Clear methodology papers on data collection for fitness, walking and functional outcomes in PAD to aid the uniformity of data collection nationally and internationally • Embedding uniform outcomes into clinical trials in PAD
Big Data	• Specific PAD-focused health economics data to understand actual healthcare costs for PAD	• Studies on cost-effectiveness of surgical vs pharmaceutical vs exercise interventions
Implementation and Policy	• Delivery of information to patients for secondary prevention of cardiovascular disease postsurgical procedures • An understanding of the needs of patients with PAD and what would enable participation and adherence to exercise programs and best medical therapy	• Improved communication to medical practitioners to encourage greater compliance with best medical therapy for risk factor control • Establishment of PAD consumer groups involving clinicians, researchers and patients with PAD to improve consumer engagement and awareness of PAD risk factors, management, and secondary prevention

Abbreviations: ACvA: Australian Cardiovascular Alliance; PAD: peripheral artery disease; QoL: quality of life.

bypass surgery [20] (low-density lipoprotein [LDL] cholesterol <1.8 mmol/L, systolic blood pressure <140 mmHg, smoking cessation, antiplatelet therapy) despite evidence that this medical treatment reduces the median 10-year risk of major CV events by 29% [21]. With this gap in care post surgery, and most patients with PAD not being on best preventative medical therapy [11,20,22], Australia must look to ensuring that patients with PAD are provided best preventative medical care through the use of statins, anti-thrombotics, and hypertension and diabetes treatments [23,24], to improve patient outcomes.

Disease Mechanisms

Mechanisms of PAD are not yet completely understood. Preclinical models such as the hindlimb ischaemia model in animals only partially reflect the biology and systemic comorbidities associated with the clinical presentation of PAD, and further efforts are needed to include the impact of diabetes and age [25]. Emerging evidence highlights sex differences in PAD, with women being asymptomatic or having atypical symptoms and facing poorer treatment outcomes to men [26–28]. There is a major knowledge gap in understanding women's CV health in PAD which is heightened by 71% of preclinical-studies exclusively using male animals [29], and only ∼25% of participants in PAD-related clinical trials over the last 10 years were women [26]. Indeed, the recent 2024 European Cardiology Society's key message in gaps in evidence relates to sex differences in PAD [30]. More studies are needed to understand sex differences in PAD pathophysiology, treatment and patient care.

Recent studies in humans highlight differences in the pathophysiology of atherosclerosis-related clinical events in peripheral arteries, compared to the coronary vasculature. This includes a greater role of thrombosis in chronic PAD compared with chronic coronary artery disease (CAD) [31,32], and impaired microvasculature function. Insights have come from skeletal muscle biopsies in PAD patients, showing evidence of capillary rarefaction [33], ultrastructure alterations of capillaries and basement membrane enlargement [34], associated with altered microvascular blood flow [35] and impaired walking capacity [33,34]. Such microvascular dysfunction increases amputation risk by ∼20-fold and warrants further study [36]. Mechanisms of susceptibility to PAD in humans could be revealed through unbiased discovery and multi-omic approaches in both blood and plaque in well-characterised patient cohorts [37].

Drug Discovery and Translation

While there have been substantial advances in clinical outcomes seen with new anticoagulant therapy, and agents achieving more dramatic LDL reduction, there is a need for drug therapies to enhance tissue perfusion, improve blood flow, and reduce ulceration and gangrene.

Recent randomised control trials (RCTs) [38,39] have demonstrated the direct benefits of oral anticoagulants in reducing the incidence of acute limb ischaemia or major amputation, and the benefits of aggressive LDL lowering with the proprotein convertase subtilisin/kexin type nine inhibitor, Evolocumab [40]. However, more effective medical options are needed to improve symptoms and reduce complications related to ischaemia. One (1) medication—the vasodilator and antiplatelet agent cilostazol—has been shown to improve symptoms and functional impairment related to intermittent claudication [24,41], but it is not widely available in Australia due to its limited effects on walking ability and contra-indication in many patients [42,43].

To date, therapies enhancing angiogenesis have generally been unsuccessful in PAD [44]. However, Australian researchers have discovered and begun to translate opportunities for repurposing "old" drugs for PAD patients. An example includes stimulating the β3-adrenergic receptor with a clinically available drug used for bladder instability. This protects against eNOS uncoupling and improves redox balance, endothelial function, angiogenesis and limb perfusion including in a diabetic model [25]. Provisional patents for use, as well as delivery approaches have been filed (PCT/AU2022/050129 and PCT/AU2020/050130), and a clinical trial initiated [45]. Kavurma and colleagues have led an extensive body of preclinical work pointing to the TNF-related apoptosis-inducing ligand (TRAIL) pathway as a therapeutic target to improve endothelial function, tissue perfusion and function and to reduce inflammation and atherosclerosis progression [46,47]. The observed lower levels of circulating TRAIL in patients with atherosclerosis [48], and diabetic patients with foot ulcers [49], point to a potential protective role. Kavurma and colleagues' most recent discovery demonstrates that TRAIL is released by the endothelium in ∼60% of the healthy circulation, and its expression and secretion is suppressed in PAD, contributing to endothelial cell dysfunction. Furthermore, the TRAIL-receptor-2 agonist, Conatumumab, used in clinical trials to kill cancer cells, was identified as a highly promising drug candidate for improving endothelial cell function in PAD [50]. Metformin may also be an effective treatment for repurposing [51–53], promoting arteriogenesis and angiogenesis [51–53], improving microcirculation function [54–56] and muscle metabolism [57,58] as well as ambulation [59] in preclinical models. Golledge et al. [17] are now conducting a randomised controlled trial (RCT) to evaluate the potential benefits of 6 months metformin treatment on walking ability in PAD patients (Trial 9; ACTRN12618001186246; Supplementary Table 1). This trial will provide high-level RCT evidence on the efficacy and cost-effectiveness of a widely available and cheap medication which has great potential to improve walking ability, prevent functional decline and promote better quality of life (QoL) in a patient population with limited treatment options.

Collaborative biobanks of patient plaque tissue (e.g. end-arterectomy specimen) and blood, human multi-cellular

organoids [60] and enhanced integration of clinical and imaging data will bolster drug discovery and translation efforts for PAD. Aligning this with advanced omic technology platforms, bioinformatics, machine learning and artificial intelligence will add value.

Biomedical Engineering

Imaging and physiological assessment of flow in major vessels, microvasculature, and the ischaemic tissue itself, has the potential to improve personalised management of PAD. Advances in computerised tomography (CT) angiography and duplex ultrasound have been the mainstay of imaging over more than a decade but continue to benefit from engineering advances such as multi-detector row for higher spatial resolution, and most recently the "photon-counting" CT. Magnetic resonance imaging offers improvements regarding assessing perfusion under both rest and stress (exercise equivalent) conditions [61] although this is not routine in clinical practice. There is still a clinical demand for real-time tissue perfusion devices that could be used at the bedside or in the operating theatre. Various techniques including laser speckle contrast imaging, micro-lightguide spectrophotometry, functional near infrared spectroscopy, skin perfusion pressure, plantar thermography, and contrast enhanced ultrasound [62] are being explored for this purpose. Intravascular imaging (ultrasound and optical coherence tomography), and pressure/flow wire technology have also been applied to guide percutaneous interventions. Continued advancements in imaging and physiology assessment techniques could enhance the efficacy of phase II clinical trials and the evaluation of novel drugs directed at enhanced tissue perfusion.

Surgical and percutaneous revascularisation procedures are an area of substantial bioengineering advance. Revascularisation in PAD has evolved from predominantly open arterial graft and bypass operations to endovascular procedures, often adapting technologies developed initially for the treatment of CAD. Despite initial success using balloons and stents, longer-term vessel patency and distal tissue survival has been challenging. While drug-eluting (paclitaxel) stents lowered restenosis rates by more than half compared to ballon only angioplasty [63]), the drug has been implicated in increased amputation rates [64,65], with a meta-analysis identifying increased all-cause mortality [66]. Subsequent studies have contradicted the suggestion of increased mortality [67,68], but the controversy highlights that the fundamental approach of locally delivering cytotoxic drugs to treat PAD may not be without risk. Development of alternative therapeutic approaches that reduce this risk [69], target inflammation and focus on vessel healing is needed. Bioengineering advances have also contributed to minimally invasive approaches to address calcified atherosclerosis that resists intervention with balloons and stents alone, including atherectomy with rotating cutting blades or lasers [70], and intravascular lithotripsy using a specialised balloon catheter [71].

Precision Medicine

Disease stratification in research, and increasingly in clinical decision making, can be based on imaging, molecular phenotyping and clinical features. This may range from influencing decision making about who is most likely to succeed with a conservative non-surgical approach and who is likely to fail despite interventional approaches ("precision revascularisation"), through to patients who have specific phenotype that is shown to be successfully targeted by novel or repurposed treatments in the future. Balancing risk factors predicting adverse limb events vs bleeding may continue to evolve with incorporation of more genetic and molecular features in the future.

The burden of PAD on women is increasingly recognised. Compared to men, women are at a higher risk of graft failure or limb loss, experience greater functional impairment, and have reduced long-term survival after revascularisation. For women with diabetes, there is increased postsurgical mortality [72]. Women are also less likely to receive timely diagnosis or be adequately screened, often due to asymptomatic or non-specific symptoms [72]. We need to increase the number of women in PAD trials to understand potential sex differences in treatment responses.

Exercise Management

Structured exercise programs have been shown to be consistently effective in patients with PAD [73–76] and are strongly recommended as first-line therapy based on class 1A evidence [18,77–79]. Despite the positive effects of exercise on walking capacity and symptoms in patients with PAD and intermittent claudication [3,13,24,74,76,80], equitable access to exercise therapy is limited by the availability of dedicated programs, as well as low referral and uptake [80,81]. Several key clinical trials of exercise therapy in Australia include the effects of a comprehensive multidisciplinary rehabilitation program such as CV rehabilitation in patients with PAD (See Supplementary Table 1, Trials 1 and 3). Audits and surveys of patients and healthcare workers investigating why access to exercise programs is limited and under-funded, and what would enable participation are also needed. This is currently being investigated with Askew and colleagues [78] (See Supplementary Table 1, Trial 6).

There is a need for further research to better understand the mechanisms of action of exercise in patents with PAD, as well as the optimisation of prescriptive elements including exercise intensity, the format (e.g. intervals) and mode of exercise, and to improve participation in both supervised and non-supervised programs. Research on the effects of exercise in patients with severe disease and amputation is also lacking, and consideration of exercise options for those

with prosthetic devices is required. Further studies are needed combining exercise with endovascular treatment [82,83]. Additionally, potential rehabilitation solutions that may mimic the effects of exercise, including passive limb movement, intermittent pneumatic leg compression therapy, vibration therapy, and neuromuscular electrical stimulation, have shown early benefits on haemodynamics and walking ability, but need further investigation. Askew and colleagues are currently investigating the effect of neuromuscular electrical stimulation, and we look forward to seeing the results of this clinical trial (Supplementary Table 1, Trial 5)

Exercise is generally considered a safe and reliable preventative option to reduce long-term complications and care costs, but it is understudied as an intervention in those with profound disease and amputation and the mechanism of action is still not clearly understood. It is also poorly funded and there is inequitable access to services across Australia.

Clinical Trials

Australia has played leading roles in both investigator-initiated, and industry-supported trials relevant to PAD, both surgical and non-surgical. The current clinical trials underway in Australia are outlined in Supplementary Table 1 and aim to establish the formation of a national clinical trial platform for patients with PAD. Australian researchers have also formed strong collaborations with international researchers, including in the United States, Europe and the United Kingdom. Key collaborations on clinical trials from Supplementary Table 1 include those by Askew and colleagues (Supplementary Table 1, Trial 5: ACTRN12621001383853) and Golledge et al. [17] (Supplementary Table 2, Trial 9: ACTRN12618001186246). It is hoped that further collaborations will continue to develop internationally providing an impressive foundation for the future of PAD research in Australia.

The Star-PAD trial (Stimulating β3-Adrenergic Receptors for Peripheral Artery Disease; Supplementary Table 1; Trial 2; ACTRN12619000423112) [45] was built from the fundamental research discovery discussed above and is an excellent example of drug repurposing to achieve improved tissue perfusion. The ACvA PAD Working Group have identified the advantages of establishing a national registry of PAD patients ideally populated via linkage to electronic medical records and administrative datasets, with potential to support efficient and innovative embedded clinical trials. This would be valuable to both investigator-led and global industry studies.

Big Data

Australian-specific evidence from large cohorts with PAD is limited and needs harmonising. This is critical for understanding gaps and inequities in access to best evidence-based treatment and outcomes. Aligned with the ACvA's work to establish the National CV Health Leadership Research Forum, we will work to identify and achieve national consensus on a minimum set of clinical quality indicators and outcomes that will be the core for registries and dashboards. The use of routinely collected electronic health data presents a strategic opportunity to gather population-wide outcomes on PAD. National policies on information sharing and data-linkage services have increased the availability of clinically useful population-wide databases for researchers [84,85]. Creating a link between routinely collected data in clinics and a detailed national data registry is key for future research and guidance of future trials. Therefore, strong partnerships with clinicians, policy makers and researchers using routinely collected health data need to be developed to ensure research questions are achievable and to facilitate translation of findings into health policy and practice. Existing PAD registries and audit databases (such as the Australian Vascular Audit) can be linked to routinely collected health datasets to expand the range of clinical outcomes and length of follow-up. New PAD registries and clinical trials should ideally include a plan to enhance monitoring of patient outcomes through data-linkage. As methods for real-time linkages in big data evolve, these data can be used to support clinical decision making and risk prediction.

National PAD registry data will help to answer further questions around exercise prescription for the individual patient, responder vs non-responders and whether location and severity of disease play a role in response. A registry detailing exercise and secondary prevention services for PAD, including cardiac rehabilitation programs that treat patients with PAD would be beneficial and provide a source of highly valuable, high-quality data.

Other questions that could be answered through access to large data sets are outlined in Supplementary Table 2.

Implementation and Policy

When current guidelines in treatment and management of PAD are reviewed it is important to report on uptake of these guidelines and availability of, and funding for recommended specialities such as supervised exercise programs. Current best medical therapy recommends exercise as gold standard; yet, the availability, referral to and uptake of such exercise programs in Australia is very low [80,81]. From an implementation perspective, supervised exercise programs are not widely accessible in Australia. Patients are rarely referred to these programs, there is inequity of availability, and they are not funded by the Federal government. Analysis on real-world compliance with these programs is needed, as well as reviews and comparisons of global guidelines vs Australian guidelines. Cardiac rehabilitation is successful in Australia for patients with CAD. We need to explore why patients with PAD are not automatically funded under the Australian Medicare system for the same program.

Further research is needed, specifically focusing on gaps and inequities in access to treatment across Australia's diverse population. Thorough analysis on treatment compliance in rural and regional areas vs metropolitan areas,

First Nations Australians vs non-First Nations Australians, and in areas that experience socioeconomic disadvantage compared to areas that do not, is needed to help us identify which populations we need to target. Research is needed to identify how we can improve health outcomes for First Nation Australians, and populations living in rural and regional Australia as well as within patient-level disparities (including culturally and linguistically diverse patients, patients with severe mental illness and multimorbidity).

Value-Based Care

Across a range of health systems, not just within Australia, there is a shift to deliver value-based healthcare aiming to deliver better outcomes for patients in a way that is financially sustainable and considers the patient and clinician experience. Importantly, value-based healthcare is not about cost reduction, but rather resource prioritisation and investing in healthcare that delivers a clear value proposition. Standardised summary measures like incremental cost-effectiveness ratio (ICER) offer decision-makers with a benchmark that considers both costs and outcomes. For example, the costs and outcomes of treating PAD using an exercise intervention can be compared to endovascular interventions or even treatments across other conditions, in a way that is impartial.

Two common methods of evaluation that should be considered for PAD include cost-effectiveness analysis (CEA) and cost-utility analysis (CUA), both of which use ICERs to compare treatment alternatives. CEA measures outcomes in natural health units such as deaths or MACE prevented, or minutes of physical activity achieved. CUA measures outcomes in quality adjusted life years, disability adjusted life years, or health adjusted life years, combining survival with QoL, measured using various instruments [86]. There is a lack of evidence in these areas for PAD in Australia. Prospective planning and data collection is needed from the early planning stages to assess the health economics of new PAD interventions and treatments. The use of patient-reported outcome measures and patient-reported experience measures are complementary for delivering value-based healthcare [87] and can be used directly in the calculation of health related QoL in CUA.

The economic benefits of increasing physical activity at a population level have been known for over a decade. In 2011, Cadilhac et al. [88] reported a feasible reduction (10%) in the prevalence of physical inactivity could lead to total potential opportunity cost savings of AUD$258 million. The potential impact in health sector costs was estimated to be AUD$96 million in savings. The use of rivaroxaban plus aspirin over aspirin alone was deemed cost-effective (defined as ICER <£20,000/quality adjusted life years or ~USD$25,000), even after adjusting for the increase in major bleeding events [89]. There is considerable variability in healthcare costs across countries that make these findings difficult to apply to an Australian context, hence further modelling should be undertaken.

Consumer Engagement

The ACvA PAD Working Group is pro-active in engaging consumers, those living with PAD and stakeholders in the codesign of research and translation, as well as in advocacy for research and participation in trials. We have established that one area of need is raising awareness around management and prevention of disease progression among the affected cohort. The design and implementation of a patient registry is important to provide patients, as well as their treating physicians with details of clinical trial options as a uniform part of treatment.

As the popularity of social media continues to grow, it is important to establish a network to raise awareness of PAD, focusing on prevention and treatment options. Promoting healthy lifestyle choices through social media is essential. It is important to establish an evidence-base for such programs in PAD, particularly to reach those that are house bound with poor mobility. Engaging persons with daily lived experience of PAD, can raise awareness and elevate real-life concerns, help devise the most targeted solutions and assist with meaningful community engagement. Our community needs greater awareness of PAD risk factors, management options and therapies for secondary prevention and the ACvA PAD Working Group is proud to include consumers in the activities of the group, and highly values their opinions and experiences.

Conclusions

Novel, non-invasive approaches to improve patient care, health outcomes, mental and physical QoL; reduce hospitalisation, and avoid death, are urgently needed for patients with PAD. Despite excellent clinical care in Australia, there are major unmet needs faced by patients with, or at risk of, developing PAD. This paper brings together gaps identified in discovery science, new diagnostics, drugs, devices, and therapeutic strategies across PAD in Australia and presents potential solutions, including the development of a national registry to use the immense value of collaborative data. Partnership with consumers, health economists and policy experts will ensure impact is measurable and ongoing sustainable approaches are developed to ensure Australian's receive world's best care. A focus on the patient priorities across Australia's diverse population, including ensuring all patients, surgical or not, receive optimal medical therapy will allow for the greatest impact targeting those with the greatest need. Furthermore, collaboration between consumers, clinicians and researchers both nationally and internationally combined with Australian national and state dataset collaboration will greatly enhance Australia's delivery of medical care to this diverse patient population. To assist with the management of PAD in Australia, a future systematic/narrative review of approaches to PAD management in Australia compared to internationally is warranted.

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Declaration of Competing Interests

There are no conflicts of interest to disclose.

Author Contributions

B.P., G.F.: Conceptualisation; Roles/Writing - original draft; and Writing - review & editing. M.K., S.W., J.G., C.As., A.H.: Roles/Writing - original draft; and Writing - review & editing. T.R., C.Ab., S.A., M.G., S.S.: Roles/Writing - original draft.

Appendices

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