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Summaries

Complementary and Alternative Medicine (CAM): use and views among patients with solid organ and haematological malignancies in Northland, New Zealand

Edmond Ang, Vincent Newton, Lisa Dawson

Complementary and alternative medicine (CAM) is a diverse group of therapies outside of standard medical care. In this study, we used a simple questionnaire to explore CAM use and views among patients who were attending their doctor's appointment or receiving treatment at a public cancer care facility.

Pharmacologic therapy among patients with type 2 diabetes mellitus admitted to the cardiology service

Evelyn Lesiawan, Thomas Seaton, Jocelyne Benatar, Jithendra B Somaratne

Our study focused on patients who were admitted under the cardiology department at Auckland Hospital with type 2 diabetes mellitus. One in five patients admitted under our service had diabetes and medications are often not optimised during their hospital admission. Pacific patients made up a large proportion of the patients in our study which suggests they are at high risk of both diabetes and heart disease. Empaglifozin is a new medication available in New Zealand that improves both cardiovascular and renal outcomes. Thus, clinicians should be comfortable with the initiation and titration of this medication.

The incidence of symptomatic venous thromboembolism following orthopaedic surgery at Bay of Plenty District Health Board

Joshua Read, Andrew Vane, Dawson Muir, Frances Stringfellow

Following major leg surgery, there is a 1.5% risk of developing blood clots. These are either clots in the legs (deep vein thrombosis) or in the lungs (pulmonary embolism). These most commonly occur within 2 weeks of surgery. Patients that go to the intensive care unit after their operation, and those who have heart disease, are more likely to develop blood clots. Despite using blood thinning medications, clots can still occur.

Longitudinal trends in community antibiotic consumption in the Waitaha Canterbury Region of Aotearoa New Zealand over 10 years (2012–2021): an observational study

Nienke N Hagedoorn, Ibrahim Al-Busaidi, Paul Bridgford, Sharon J Gardiner, Tony Walls, Ben Hudson

Antimicrobial resistance is an important cause of global mortality and one of the main drivers for antimicrobial resistance is overall antibiotic consumption in the community. From 2012 to 2021, we found that community antibiotic consumption decreased by 30% in Waitaha Canterbury. These changes align with antimicrobial stewardship guidance which encourages more careful use of antibiotics.

Percutaneous vertebroplasty: efficacy in the management of pain related to acute vertebral compression fractures

Ashreya Duvuru, Stewart Paul Hawkins

Percutaneous vertebroplasty (PV) is a minimally invasive procedure in which bone cement is injected into a fracture of the spine. This retrospective study analyses PV in patients with intractable pain from such fractures, often elderly women with bone thinning. The study showed that the procedure was highly effective in pain management. The article also discusses patient selection and why the technique is under-utilised.

Cardiac complications of COVID-19 infection

Sharan Randhawa, Ammar J Alsamarrai, Simon Lee, Jithendra B Somaratne

COVID-19 infection can lead to the development of heart complications during the initial illness phase. These complications include heart attack, inflammation of the heart (myocarditis), blood clots, dangerous heart rhythms (arrhythmia), and heart failure. Patients with COVID-19 who develop heart complications tend to do worse than everybody else. Some patients who recover from the initial infection go on to develop persistent symptoms after they have recovered. This is called long COVID. Not much is known about this yet but it affects anywhere from 5–10% of people, and possible more.

Protecting school communities from COVID-19 and other infectious disease outbreaks: the urgent need for healthy schools in Aotearoa New Zealand

Amanda Kvalsvig, Belinda Tuari-Toma, Carmen Timu-Parata, Julie Bennett, Claire Sinnema, Jennifer Summers, Cheryl Davies, Constanza Jackson, Andrew Dickson, Lucy Telfar Barnard, Michael G Baker

Aotearoa New Zealand's Omicron outbreaks demonstrated that widespread COVID-19 transmission in schools is harmful to both health and education. School should be one of the safest places a child can be. Instead, the events of 2022 showed that New Zealand schools continue to be high-risk settings for infectious disease transmission. High COVID-19 infection rates in school teachers indicate that their occupational safety has been significantly compromised by the lack of protections in schools. This unacceptable situation is preventable in the future, but it requires reorientation away from the current "business-as-usual" approach to a science-led and whānau-centred community response.

In this editorial we review evidence and on-the-ground experience that emerged during 2022, and propose a set of goals and actions to protect students, staff and whānau from the inequitable impacts of COVID-19 and other infectious diseases. As well as protecting health and learning during outbreaks and the winter months, cohesive and effective infection control practices embedded within school communities can avoid a situation where schools act as early amplifiers of a new, severe pandemic disease.

The adverse impacts of COVID-related education policies and guidelines in 2022

In January 2022, Aotearoa New Zealand prepared for the imminent onset of its first Omicron variant outbreak, which meant widespread population exposure to SARS-CoV-2 infection (the virus that causes COVID-19) for the first time. The Government announced that the priority for children was in-person learning.[1] However, schools were unprepared to mitigate the spread of this highly infectious pathogen: New Zealand children were at best partially vaccinated, and key indoor air quality equipment had not been delivered.[2] As the outbreak progressed, further removal of infection control measures, particularly contact tracing, meant that schools were unable to track the progress of local outbreaks and were not resourced to protect their communities.

This approach was strongly criticised by health and disability experts. In April 2022, with high COVID-19 infection rates occurring throughout New Zealand, the Human Rights Commission published an inquiry report stating that the Government response to the spread of Omicron had put the wellbeing of disabled people at risk, and highlighting the lack of support in education settings.[3] The Inquiry's recommendations included a call to ensure access to distance-learning technology if disabled students chose to self-isolate to protect themselves and their whānau from the risks of COVID-19. The Disability Rights Commissioner also called for the Government to protect disabled learners and whānau during high transmission periods by reinstating mandatory mask wearing in schools and providing high-quality masks to students, with exemptions for those unable to wear masks.[4]

These recommendations were not implemented and policies at New Zealand schools continued to emphasise in-person learning; when families opted to keep children at home these absences were recorded as "unjustified". When colder weather arrived and schools in colder areas raised concerns about keeping windows open to ventilate, inconsistent approaches to masking and uneven provision of carbon dioxide (CO_2) monitors and air filters meant that few strategies were available to prevent infection transmission

in school settings, particularly in schools that had less access to resources.[5,6] Predictably, schools experienced high COVID-19 case numbers.

Although few New Zealand children had experienced COVID-19 at the start of 2022, during the 5 months from February to June 2022 official figures showed that there were 218,206 reported COVID-19 cases in 10–19-year-olds: around one third of the total age group. The more rigorous WellKiwis cohort data showed that 46.4% of 5–19-year-olds tested positive between February and June 2022, and this figure rose to 66.3% by the end of September.[7] Long COVID prevalence was not measured. Consistent with international studies showing that education is a high-risk occupation in the pandemic,[8] data provided to the Government on 27 July 2022 showed that New Zealand school teachers and child carers occupied, respectively, the first and second highest positions in rankings of COVID-19 rates by occupation. By that time, an estimated four in 10 school teachers had tested positive.[9] These results were not made public at the time.

Paradoxically, the policy emphasis on face-to-face learning meant that a number of schools were unable to continue teaching through outbreaks because of high levels of illness among students and staff. A September Cabinet paper stated that "*The impacts of COVID-19 on the education system are significant and ongoing*".[10] Despite the best efforts of educators to mitigate these impacts,[11] at the end of 2022, students entered NCEA exams with fewer credits than in the previous two pandemic years. This reduction in educational attainment has the potential to generate a substantial lifecourse disadvantage for the pandemic generation.

Preventing infectious disease transmission in schools

We are now in the fourth year of the pandemic and it is well established that COVID-19 infection is transmitted within school settings and spreads from schools into homes,[12–16] causing widespread impacts in school communities as experienced in New Zealand during 2022. This evidence aligns with pre-pandemic knowledge about other infections where school transmission contributes substantially to disease incidence, including influenza,[17–19] respiratory syncytial virus (RSV)[20] and measles.[21] By July 2022, internal New Zealand agency advice to the Government had acknowledged the link between school term dates and COVID-19 cases.[9]

In common with pre-pandemic childhood infections, COVID-19 case levels in schools do not simply "reflect" community transmission: in-school transmission helps to drive outbreaks. Studies in the US have consistently shown lower case numbers in schools when mask policies are in place.[22–24] In one such study that conducted paired measurements of community and school case rates, COVID-19 rates in staff and students were initially higher than in their local community, but following the introduction of a mask requirement the case rates in schools decreased to become lower than community case rates.[23] This finding illustrates the important role that schools can play in slowing the spread of community outbreaks, particularly now that the effectiveness of good indoor air quality is well understood.[25]

It is essential that school policy is based on robust risk assessment and risk management, taking into account cultural, economic and environmental factors that are relevant to each region and school. The New Zealand Government's school policy during 2022 leaned heavily on a single January 2022 report that stated that schools were not a major driver of COVID-19 transmission when other settings were open and that persisting symptoms in children resolved by 8 to 12 weeks.[26] Unfortunately, some more cautious messages in the body of the report were diluted in accompanying media statements, which reassured the public that COVID-19 was mild in children. These statements did not mention long COVID and other potential longer-term effects of this infection; the health and financial impacts that occur when COVID-19 is brought into a household from the school community; or the occupational risk to school staff.[27] This over-optimistic risk assessment impeded the efforts of health and disability advocates to reduce transmission in schools.

Why school transmission matters: COVID-19 health impacts in children

There is now abundant evidence of short- and longer-term health impacts of COVID-19, indicating the potential for significant population health impacts when children and those closest to them are widely infected and reinfected.

We focus here on health impacts for children, but as noted above, teachers have a high occupational risk of COVID-19 infection and data from the UK show that they also have an elevated risk of developing long COVID.[8] The effect of school transmission

Table 1: Health impacts in children following COVID-19 infection: current state of evidence.

Serious and fatal outcomes
COVID-19 infection has lower hospitalisation and mortality rates in children compared with adults, but when virtually all children are exposed, the population impact on children becomes substantial. US figures show that COVID-19 is now the leading infectious and respiratory cause of death in school-aged children, ahead of many other diseases where vaccines are routinely used.[28]
Development of new health conditions following infection
An estimated 65 million people have long COVID,[30] including children. Research is currently underway in New Zealand to investigate long COVID in children following the Omicron outbreaks of 2022. The underlying mechanisms of long COVID are now better understood, although there is much work to be done.[31] Examples of documented health concerns in children include: Multiple impacts on the brain in childhood ranging from common to rare, including fatigue, cognitive deficits, stroke and new psychiatric conditions[32] with hypometabolism of key areas of the brain seen on functional imaging;[33] Increased risk of cardiorespiratory symptoms and disease, again ranging from common (breathlessness) to rare (cardiac thrombosis); for myocarditis, vaccines show a protective effect relative to disease;[34–36] New-onset diabetes;[37,38] and A large number of other effects; see this major 2023 review[30] and other studies.[39,40]
Evidence of sub-clinical or latent organ damage
Children generally have good functional reserve and may tolerate organ damage with no or minimal symptoms. However, some types of tissue damage during childhood raise concerns about health impacts in later life.[42,43] Clinical research continues to identify biomarkers of tissue damage, including in well children who had mild COVID-19 infection. Child-specific examples include: Studies using specialised lung function tests show persisting abnormalities in lung function after recovery from the initial COVID-19 illness;[43,44] Coagulation biomarker studies show abnormal clotting profiles;[45] Persisting changes in cardiac function were observed in 60% of a cohort of previously healthy children who had had a mild or asymptomatic episode of COVID-19 infection; average follow-up time was 148 ± 68 days;[46] and Viral persistence in tissues is well established in adults, and is now demonstrated in children.[47]
Immune dysregulation
Alterations in immune function following COVID-19 infection are well established and raise the risk of COVID-19 re-infection, susceptibility to other infections and other health impacts. Examples include: Longitudinal studies of immune responses show rapid clearance of SARS-CoV-2 virus in children and a lack of robust memory T-cell responses relative to adults; this pattern of response could explain children's relatively less severe symptoms in the early phase, but it may compromise their ability to resist reinfection;[48] Longer-term (8 months post-infection) immune dysregulation in adults[49] with corresponding child results awaited (but see results below); COVID-19 causes immune cells to switch their gene expression profile from immune to pro-thrombotic (clotting) signatures,[50] consistent with increased risk of thrombosis in children;[51] Impaired gut and respiratory microbiomes have been observed following COVID-19 infection,[52] as another potential mechanism for ongoing health issues; Of particular relevance to New Zealand (where Group A Streptococcus [GAS] infections and rheumatic fever rates are high and inequitable) is evidence that GAS coinfection can contribute to COVID-19 severity;[53] and Additionally, COVID-19 infection is associated with increased risk of GAS infection from 4 to 8 months later.[54]

on the health of household members is unmeasured in New Zealand's COVID-19 data but community providers are seeing substantial impacts such as reduced work hours for parents needing to stay home and care for tamariki. Māori and Pasifika are more likely to be living in large multi-generational households, with potentially serious impacts when COVID-19 is introduced to the home environment. COVID-19 appears to be similar to a number of other infections, such as RSV, that are introduced into households by school-aged children and can cause serious illness in the youngest and oldest household members.[20,28]

We have previously reviewed the evidence about longer-term impacts of COVID-19 infection in children.[29] Table 1 lists some illustrative examples from the current evidence. The list is not exhaustive as this is now a very large scientific literature.

Next steps for better protection in New Zealand kura/schools: goals and implementation

The COVID-19 pandemic has caused significant loss of education time in New Zealand and beyond,[24] highlighting the importance of protecting health to protect learning.

The duty of care to children and communities

The Crown has a Treaty duty to adopt rational, scientific, equitable policy choices for Māori that sustain Māori wellbeing.[55] Māori have already asked in several ways to be a part of the decision-making around planning and implementing COVID-19 measures and have alerted the Government when it has fallen short.[56] Māori voices need to be safely heard (with respect to anti-racism), followed by actions so that schools are supported to offer healthy spaces for learning. Healthy schools also protect the whānau at home and the wider hapori/community; kura/schools increasingly serve as a focus within communities for meetings and group events, and remain a hub for whānau seeking primary healthcare assistance, including access to pandemic response information and resources.

Instead of devolving key strategic decisions for individual schools with varying access to information and resources, the safety of children in schools should be universal and rights-based, ensuring protection under the Convention (UNCRC) and the Declaration on the Rights of Indigenous peoples (UNDRIP). These international frameworks complement and support upholding the intended constitution of Te Tiriti o Waitangi and the obligations of the articles, providing the active protection of tino rangatiratanga, kotahitanga, ōritetanga and mana.

Ministry of Health Te Tiriti o Waitangi goals include: mana Māori = enabling Māori customary rituals framed in Te Ao Māori, encapsulated within mātauranga Māori and enacted through tikanga Māori; mana tangata = achieving equity in health and disability outcomes for Māori across the lifecourse and contributing to Māori wellness; and mana motuhake = enabling the right for Māori to be Māori and to exercise self-determination over their lives and to live on Māori terms according to Māori philosophies, values and practices including tikanga Māori.

The need for a cohesive public health approach

There is both a need and an opportunity for New Zealand to implement a cohesive approach to protections against COVID-19 and other infections, building on the many synergies in this area.[57] For example, good indoor air quality enables concentration and therefore productive learning as well as protecting against COVID-19 infection and a large array of other respiratory infections.

Similarly, a well-resourced and accessible system for online or hybrid learning may be needed during a large COVID-19 outbreak or during extreme weather events such as the recent North Island flooding. Such a system should also include funding for outreach services to support ongoing access and engagement. Low childhood vaccination levels and the current high probability of a measles outbreak additionally indicate the need for a robust online learning system to support previously unvaccinated contacts during an active measles outbreak, when they may be requested to quarantine from 7 days after first exposure until 14 days after their last exposure.[58]

These protections should be embedded within the school system and within New Zealand's next pandemic plan as they may be needed each year during the winter respiratory season or at short notice during a public health emergency.

The need for a practical, science-informed action plan

In New Zealand and elsewhere, highly effective public health and social measures are under-utilised through lack of implementation and evaluation. In the fourth year of the COVID-19 pandemic, this evidence gap has been declared

a "pandemic tragedy".[59] The Bulletin of the World Health Organization (WHO) has called for studies to support better implementation of these important protections.[60]

New Zealand is well positioned to contribute to this evidence base by embedding and evaluating best practice models in schools. In the housing sphere, New Zealand researchers have delivered world-leading community trials of healthy housing interventions that provide actionable evidence for policy, including showing that healthy homes help to reduce days off school.[61] Similar principles and approaches can be used to optimise the safety of school communities and protect access to education.

Table 3 (Appendix) lists key goals for infection control and proposes an array of school-based initiatives aimed at protecting staff, students and whānau from the impacts of COVID-19 and other infectious diseases.

Conclusions

Aotearoa New Zealand's policy of "business-as-usual" school-based infection control resulted in serious and inequitable impacts on health and education during 2022. There is an urgent need for New Zealand to reorient its school policy to protect students, staff and whānau in the current era of ongoing new COVID-19 variants. Already in 2023 a school was forced to close shortly after the start of Term 1 because a high proportion of students and staff had COVID-19.[62]

School should be one of the safest places a child can be. Instead, the events of 2022 highlighted that New Zealand schools continue to be high-risk settings for infectious disease transmission. Extremely high infection rates in school staff indicate that their occupational safety has been significantly compromised by the lack of protections in schools.

Even at the milder end of the long COVID spectrum, illness lasting 3 months or more is not trivial in view of the impact it can have on children's social wellbeing and education, or on the ability of teachers and whānau to continue working. Rarer but more serious COVID-19 outcomes can be life changing and life limiting. These impacts are particularly concerning because the ongoing emergence of new variants means that immunity to SARS-CoV-2 is relatively short lived: two or three COVID-19 outbreaks per year, as in 2022, allow very little recovery time from fatigue, immune dysregulation or loss of teaching and learning days.

We have previously proposed an Action Plan for New Zealand schools.[63] In 2023 New Zealand needs to set clear goals and implement them to protect health and education in the current volatile infectious disease environment. Other pathogens including GAS are showing unpredictable patterns of spread in children and there is a high risk of measles and other outbreaks. Widespread infectious disease transmission in

Table 2: Proposed goals for a science-led and whānau-centred approach to infection control in schools (including COVID-19 and other infections).

Proposed goals for a science-led and whānau-centred approach to infection control in schools
1. Air quality in classrooms is excellent at all times; 2. Children, young people and staff are not in school while they are infectious; 3. Additional protection via masks is rapidly available during outbreaks (e.g., periods of high COVID-19 transmission and/or seasonal respiratory infection and/or an emerging influenza pandemic); 4. Schools are resourced to provide high-quality teaching and learning and other support online or in a hybrid model during infectious disease outbreaks; 5. School-based health outcomes and progress on curriculum aspirations are equitable, rights-based and uphold Te Tiriti o Waitangi; 6. School communities are well-informed and are actively participating in programmes to improve health and wellbeing; and 7. There is a high level of situational awareness throughout the school system supported with high-quality surveillance of health and the coverage of key interventions.

schools has the potential to worsen existing high inequities in infectious diseases[64] that have pervasive impacts on low-income families. Cumulatively, if not addressed, the impacts experienced in 2022 and beyond may contribute to a measurable future deterioration in the health of New Zealanders and the sustainability of the education sector. The experience with Omicron variant outbreaks also indicates a concerning gap in New Zealand's pandemic preparedness.[65] Without cohesive and effective infection control practices embedded within school communities, there is a risk that schools may act as early amplifiers of a new, severe pandemic disease.

New Zealand's approach to infection control in schools should be reorientated to be science led and whānau centred, based on a set of clearly articulated and well-understood goals (Table 2). The emphasis should be on supporting whānau-centred agency that upholds Te Tiriti articles as a means of delivering equity. These activities can be seen as placing a korowai/cloak of protection around school environments and communities.

COMPETING INTERESTS
Nil.

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Appendix: goals and implementation.

Table 3: Goals for infection control in New Zealand schools and potential projects to support effective implementation.

Goals	Implementation	Comments
Air quality in classrooms is excellent at all times	Roll out community trials of what works in the New Zealand setting, enabling the education system to monitor and sustain good indoor air quality while maintaining thermal comfort in different building types, seasons and climate areas. Establish policies. Other jurisdictions (e.g., France) have legislation to ensure appropriate ventilation standards in schools;[66] New Zealand could liaise with policy and implementation counterparts to adapt for the New Zealand context. Carry out an evaluation targeting insights into barriers and enablers for schools and teachers implementing policies and guidelines for air quality (and other mitigations including infection control and masking) effectively, consistently and equitably. Develop a public health-led tailored education package for schools around ventilation and how it works, aimed at a wide audience including whānau, students and providers who go into schools (e.g., public health nurses, community organisations, Hauora Māori providers) so that they can also become advocates. Develop a plan that includes short- to medium-term measures (e.g., portable air filtration units) that transition over time to a sustainable future of longer-term, structural changes to deliver a high standard of indoor air quality.	Optimising ventilation was shown to achieve a substantial reduction in COVID-19 cases in school settings in Italy.[67] Portable air filtration units are shown to reduce airborne SARS-CoV-2 virus.[68] A high standard of air quality protects against a large number of infectious diseases and air pollution, enables cognitive function and better learning, and reduces allergy symptoms.[69] Several research projects are currently in progress in New Zealand. School and system conditions can mean that well-intentioned practitioners cannot realise the health and inclusive curriculum goals they aspire to and the barriers to implementation are not well understood.
Children, young people and staff are not in school while they are infectious	Identify effective and acceptable protocols for schools, such as test-to-return (identifying when they are no longer infectious after isolation), test-to-stay (identifying whether close contacts of a case are infectious), and/or routine testing (to identify persons who are infectious but have no symptoms). Develop a risk-assessment system and identify specific supports that may be needed to achieve this goal, especially for children whose wellbeing is compromised when they are not in school. These assessments and support would overlap strongly with initiatives to protect children's wellbeing during the summer break (which is a much longer time away from school than any infectious disease quarantine period). Conduct trials of rapid point-of-care tests that can detect an array of other respiratory viruses as well as SARS-CoV-2.	Modelling of test-to-return options by Covid Modelling Aotearoa shows that current advice not to test is likely resulting in a high number of people with COVID-19 returning to public settings while still infectious.[70] Siblings need to be included in outbreak control planning to prevent seeding of infections into other school years and other schools. For this goal to work, negative impacts of absence must be addressed, e.g., with absence of sanctions and provision of financial and other support to students and teachers.

Goals	Implementation	Comments
Additional protection via masking is rapidly available during serious outbreaks (e.g., periods of high COVID-19 transmission and/or seasonal respiratory infection and/or an emerging influenza pandemic)	Conduct a trial and survey of high-quality child-sized respirator masks in school settings to identify enablers and barriers to mask use and test mitigation strategies, along the lines of the randomised clinical trial by Science et al.[71] Conduct a qualitative study to develop best practice guidelines for enabling access to communication when staff and students are masked, including technological and behavioural strategies (e.g., microphones and amplifiers), slower speech patterns, reduced background noise, clear face masks, written or electronic text (including live captions) and non-verbal communication (e.g., using gestures or hand signals).	The WHO advises mask-wearing for children over the age of 5 years, emphasising that "*the best interest, health and well-being of the child should be prioritized*".[72] A 2019 randomised clinical trial of a paediatric N95 mask in children aged 7–14 that measured safety, fit and comfort reported that the mask was "*well fitting, comfortable and safe for use in children at rest and on mild exertion*".[73] The trial of mask-wearing by Science et al. reported that masks were well accepted by the children, and that there was less hand-to-face contact among the children wearing masks, compared with the control goup of children not wearing masks.[71]
Schools are resourced to provide high-quality teaching, learning and other support online or in a hybrid model during infectious disease outbreaks	Conduct trials, particularly in schools in low-income areas, to identify effective and equitable strategies for resourcing online or hybrid education during a major outbreak or other public health emergency. Leverage educational networks and develop case studies that support improved quality of online learning delivery in support of goals for learners' inclusion, health and educational progress, and the wellbeing of learners and teachers. Develop a policy design project using collaboration between educators and infectious disease modellers to develop a decision framework about when it is appropriate to move to online or hybrid learning as a circuit-breaker during active outbreaks.	There is a digital divide: national infrastructure for internet access is inadequate and not every learner has access to an appropriate device for learning. Waiting until schools are compelled to close because of high levels of sickness is disruptive to both education and population health. A move to online or hybrid learning should be a planned action with a smooth transition and resources in place to protect health and learning.
School-based health outcomes and progress on curriculum aspirations are equitable, rights-based and uphold Te Tiriti o Waitangi	Identify the impact of long COVID, fatigue and pre-existing/new health conditions on school attendance and learning; communicate solutions that are proposed by students and their families. Ensure that there is formal monitoring and reporting of inequities in the school system (see below). Enable iwi and hapū interventions: for example, Ngāti Toa has welcomed a settlement with the Ministry of Education that will see it buy the land of 40 public schools in the Wellington region, negotiated under the Ngāti Toa Rangatira Claims Settlement Act 2014. Their active role in the community pandemic response along with other iwi, including supporting other mātāwaka iwi responding to the COVID-19 pandemic in the region, has further demonstrated pro-equity solutions that all iwi exhibited within their regions, that afforded and augmented opportunities to improve Crown and Māori relationship.	Impacts of the COVID-19 pandemic have been highly inequitable.[56,74] As part of Crown and Māori relationships to support obligations of Te Tiriti o Waitangi articles, Te Puni Kōkiri developed the COVID-19 Whānau Recovery Fund and is continuing to support hapū, iwi, Hauora Māori providers and organisations to facilitate a Māori-led response and recovery from COVID-19.

Goals	Implementation	Comments
School communities are well informed and are actively participating in programmes to improve health and wellbeing	Use a Citizen Science approach – develop projects with active participation by children and staff, including teaching and non-teaching staff and families. Develop a network of Kaupapa Māori research and researchers in school communities, especially Kura Kaupapa Māori, where tamariki and whānau can take on researcher roles, so that lived experience defines and leads outcomes. Develop systems for school leaders, including school boards, to access and respond to relevant data for decision making. Provide guidance and capability building for school leaders to strengthen their leadership capabilities for dealing with challenges associated with establishing and sustaining initiatives targeting these health goals. Develop and deliver learning resources for staff, students and whānau about infection control and healthy schools.	Previous campaigns about handwashing and sun safety have carried health promotion messaging beyond school settings and into communities. Initiatives developed or put in place can be embedded as contexts for young people learning the knowledge, understandings, skills, values and capabilities set out in the curriculum.
There is a high level of situational awareness throughout the school system	Establish schools as sentinel surveillance sites for monitoring incidence of infectious diseases, particularly COVID-19, respiratory syncytial virus (RSV), influenza and Group A streptococcal infection (GAS). Direct all schools to collect a set of key reporting requirements, with a subset of schools providing intensified surveillance for a range of infectious diseases, combined with collection of other in-depth measurements. Develop a system to measure and report a range of key health and learning indicators, e.g., the prevalence and impact of long COVID, inequities in health and education, days lost to education through infectious diseases and many more, where possible, linking this information into national data collections. Link school data to existing population cohorts, e.g., Growing Up in New Zealand and WellKiwis, for better understanding of household-level factors. Develop a surveillance hub to manage the surveillance and reporting functions in collaboration with other key agencies, or contract one of them to do it. Develop communication systems to ensure that school communities are always well informed about infectious disease outbreaks and are empowered to take preventive action.	A high standard of information is required for multiple purposes, including: Rapid awareness and response to community outbreaks and/or emergence of a new pandemic disease. Developing evidence-informed policy relating to schools. Evaluating the success of trials and programmes.

Complementary and Alternative Medicine (CAM): use and views among patients with solid organ and haematological malignancies in Northland, New Zealand

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ABSTRACT

AIMS: Complementary Alternative Medicine (CAM) use among patients with malignant diagnosis has been rising globally. This study assesses the prevalence of CAM among patients with solid organ or haematological malignancy at a regional outpatient cancer and blood service in Northland, New Zealand. Secondary objectives include determining: i) types of CAM used, ii) sources of information, and iii) patient perspectives on CAM.

METHOD: In this single-centre cross-sectional study, patients attending treatment or follow-up appointments at the Jim Carney Cancer Treatment Centre (JCC) between 25 September to 20 October 2017 were invited to complete an anonymous self-administered questionnaire.

RESULTS: Of the 306 assessable entries, 29% (n=89) respondents were using CAM, 10% had intentions to use CAM in the future, while 45% were undecided. Word-of-mouth (58%) was the most common source of CAM information, followed by internet sources (36%) and healthcare professionals (27%). Biologically based therapies were the most popular form of CAM used. Common reasons for CAM use include symptom relief (65%), perceived lower toxicity (62%), holistic (52%), natural (51%) and potential for cure (45%). Only 49% of CAM users felt comfortable discussing their CAM use with their oncologist/ haematologist.

CONCLUSION: CAM use is common and has relevance across oncology treatment centres nationwide. Local research into CAM use can serve to raise awareness and to assist healthcare professional training in addressing CAM use in a specific patient population.

Complementary and Alternative Medicine (CAM) is defined in New Zealand as an area of healthcare external to conventional biomedicine.[1] CAM can be used to either supplement (complementary) or replace (alternative) conventional therapy. The National Centre for Complementary and Integrative Health (NCCIH) classifies CAM into 5 categories: biologically based therapies, manipulative and body-based therapies, energy therapies, alternative medicine systems and mind-body interventions.[2] Despite attempts to define and categorise CAM, CAM is a spectrum of diverse and constantly evolving interventions. Most mind-body interventions (e.g., yoga, meditation) are harmless and widely accepted, while some CAM (e.g., acupuncture) have robust evidence for alleviating symptoms that stem from cancer and treatment toxicity. Unfortunately, a significant number of CAM are devoid of evidence and are only supported by pseudoscience.[3]

Numerous studies have reported high frequencies of CAM use among patients with malignant diagnoses.[4,5] A systematic review published in 2012 reported CAM prevalence at 40% in its patient population, although prevalence rates vary widely (34–83%) due to study methodology and variations in the definition of CAM.[6] CAM use appears to have risen over the last two decades and has developed into a multi-billion-dollar industry.[7,8] Propensity towards CAM uptake appears to be associated with the female gender, middle-age, white/European descent, higher educational/ socio-economic profile, high levels of physical activity, anxiety and dissatisfaction with conventional healthcare providers.[9–11]

The sheer number and heterogeneity of CAM presents a formidable challenge to medical oncologists and haematologists involved in cancer care. While some complementary therapies have been proven to be useful as supportive measures for patients undergoing conventional anti-cancer therapy, many are unsubstantiated and potentially harmful.[12] Risks of CAM use include potential interactions with conventional therapies, direct toxicities, unknown active constituents/

manufacturing quality and nocebo effect.[13] Most importantly, CAM users are at risk of declining conventional therapies in favour of CAM often due to pressure by family/friends, misinformation perpetuated on the internet/social media and unscrupulous marketing. Use of alternative therapy has been shown to dramatically lower survival outcomes among patients with non-metastatic breast and colorectal cancer.[14]

There is a paucity of data around CAM use among patients with a cancer diagnosis in New Zealand. In a study published by the MidCentral medical oncology services in 2003, CAM prevalence was documented in 49% of respondents with word-of-mouth being the most common source of CAM information.[15] A substantial majority of CAM users found CAM helpful while, 89% felt that CAM was safe. In another study in New Zealand utilising an anonymous telephone questionnaire, 28% of respondents felt CAM had an equal or better chance of curing cancer compared to conventional treatment, while 32% felt that CAM could be used instead of conventional therapy.[16]

In this study, we report the prevalence of CAM use among patients with a solid organ or haematological malignancy receiving treatment and follow-up at an outpatient regional cancer service in New Zealand. Secondary objectives include determining the types of CAM used, the sources of CAM information and patient perspectives on CAM.

Method

The Jim Carney Cancer Treatment Centre (JCC) based at Whangārei Base Hospital (WBH) is the sole public cancer care provider in the Northland region of New Zealand, servicing a population of close to 200,000. Northland is one of New Zealand's least urbanised and most socio-economically deprived regions, with Māori making up a substantially higher proportion of the population (31%).

An anonymous, four-page self-administered paper questionnaire was designed, piloted and modified at the JCC prior to study initiation. The domains in the questionnaire include data on i) patient demographics (age, ethnicity, gender), ii) CAM use (user/non-user or undecided, type of CAM, source of information, oncologist/haematologist informed or not), and iii) a section dedicated to exploring patient's views on CAM (reasons for using CAM, perceived safety and level of trust with oncologist/haematologist). Mind-body interventions such as yoga, tai chi, meditation, mindfulness, relaxation techniques, art, music, dance and spiritual beliefs used to enhance patient wellness were not classified as CAM in this study. This decision was made based on the acceptability, safety and utility of most mind-body interventions. The study was instead directed to address less orthodox and potentially more harmful interventions. Study participants were allowed to choose more than one type of CAM use and information source. Response to questions pertaining to perspectives on CAM were graded as agree, neutral, disagree or non-applicable.

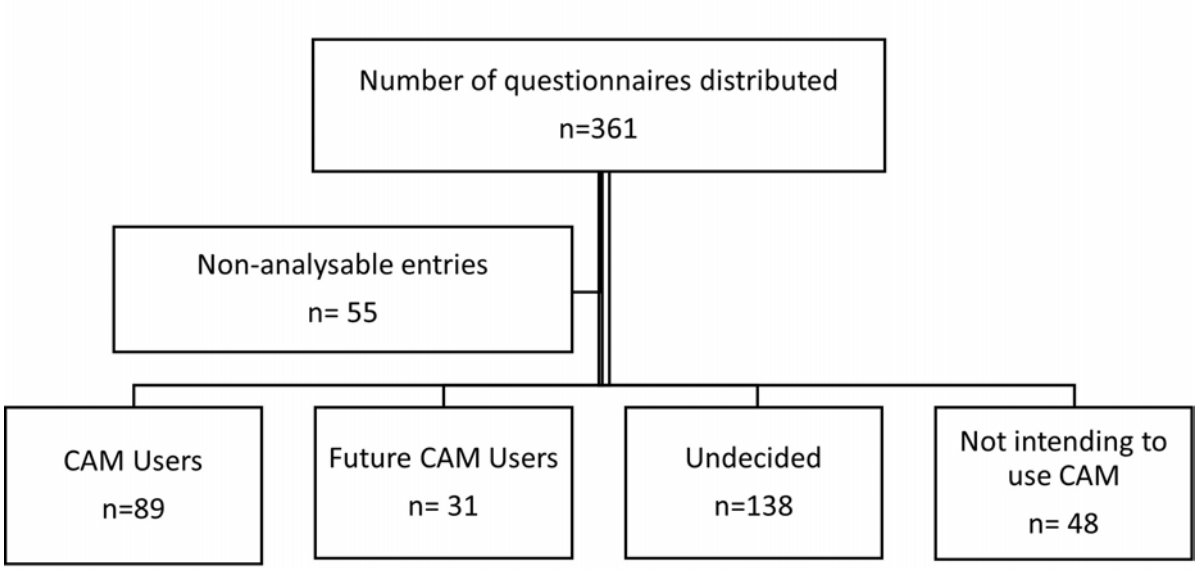
After receiving local institutional ethics board approval, all patients who attended a clinic or treatment appointment at the JCC between 25 September and 20 October 2017 were offered a questionnaire. Participation was voluntary. The questionnaire was only available in English. Patients who had difficulties reading or completing the questionnaire due to reasons of literacy or language were offered nursing or interpreter assistance. Duplicate questionnaires and incomplete entries that contained only demographic information were discarded. Data were entered into an Excel spreadsheet and descriptive statistics used for data analysis.

Results

Out of 361 responses, 306 entries had sufficient data to be included into the study analysis. Māori participation (25%, n= 78) was slightly lower than expected considering that Māori make up 30% of the Northland population and have been found to have a disproportionately higher cancer burden compared to NZ Europeans. Other ethnicities (e.g., Pacific Islander and Asian) only constituted 5% of respondents, with the rest being NZ Europeans. A total of 57% (n=174) respondents were women and the largest age group represented in this study was the 61–80-year range (61%, n=187).

Figure 1 summarises the questionnaire distribution and response based on CAM use. Almost a third of respondents were already using CAM (29%, n=89), 10% had plans to use CAM in the future while 45% (n=138) were undecided. Table 1 summarises the types and respective frequencies of CAM use among respondents. Fifty-eight percent of respondents (n=52) reported using only one CAM intervention, while seven respondents admitted to using more than three. Biologically based therapies were the most commonly used CAM (n=81). This included intravenous vitamin C (n=21), cannabis (n=16) or anticancer/detox diets (n=15). Acupuncture/

Figure 1: Consort diagram: questionnaire distribution and response based on CAM use.



traditional Chinese medicine use was also popular (n=23). Several interventions that are known to be particularly hazardous were utilised. This included miracle mineral solution, ozone therapy, colonic irrigation, chelation therapy, Gerson therapy and vitamin B17 (laetrile).

Word-of-mouth (58%, n=177)) was the most popular source of CAM information among respondents, followed by internet sources (36%, n= 110). Interestingly, 27% (n=83) of responders cited healthcare professionals as a source of information about CAM, which was more than CAM providers (15%, n= 46) and social media (14%, n=43). CAM use followed the ethnic and gender proportions of the respondents, but were disproportionately more common (71%, n= 217) in those aged under 60 years.

Among CAM users, the top five reasons for use were symptom relief (65%, n=58), perceived lower toxicity as compared to conventional treatment (62%, n=55), holistic (52%, n=46), natural (51%, n=45) and encouragement by family/friends (47%, n=42). Some users believed CAM had the potential of curing cancer (45%, n=40), were encouraged by success testimonials (37%, n=33), and felt that CAM was backed by strong scientific evidence (29%, n=26). Fifty-seven percent (n=51) of CAM users agreed with the statement that they trust their oncologist/haematologist to counsel them on CAM, but only 49% (n=44) had disclosed to their oncologist/haematologist that they were using CAM. Seventy-six percent (n=68) of CAM users supported the statement that CAM should be funded.

Of the 70 respondents that identified themselves as Māori, 30% used CAM—a similar proportion to the overall population. Māori medicine and cannabis were the most common CAM used in this subgroup. Interestingly, the largest group of respondents were undecided about CAM (n=138). Questionnaire completion rates were low for questions pertaining to views on CAM among this sub-group of respondents.

Discussion

Our study is the second published study on CAM use among patients in a publicly funded regional cancer and blood service in New Zealand. This follows the original publication by Chrystal et al. in the *New Zealand Medical Journal* on the same topic in 2003.[15] We employed a simple four-page questionnaire that was easy to understand and complete. This also allowed us to make a preliminary assessment on the types of CAM used and sample pertinent patient perspectives about CAM in our patient population.

The prevalence of CAM use documented in our study was lower than that which was reported by Chrystal et.al. and other contemporary Australasian studies. This difference could be due to differences in patient demographics (e.g., lower education/socio-economic profile) or the definition of CAM. Strikingly, a large proportion of respondents in our

Table 1: Types of CAM used and number of users.

Category	CAM	Number of users
Biological-based therapies	IV vitamin C	21
	Cannabis	16
	Detox diet/anticancer diet	15
	High dose oral vitamin C	5
	Alkaline water/Tiki Water	5
	Salvestrol	3
	Miracle Mineral Solution	2
	Ozone therapy	2
	Chelation therapy	2
	Vitamin B17 (laetrile)	2
	Gerson therapy	2
	Other supplements (herbal, purple rice, trace elements)	6
Energy therapies	Crystal therapy	3
	Electromagnetic	2
	Reiki	1
Manipulative therapies	Acupressure	2
	Colonic irrigation	2
	Reflexology	1
Alternative medical systems	Acupuncture/traditional Chinese medicine	25
	Homeopathy	13
	Naturopathy	13
	Rongoā Māori (Māori medicine)	11
	Ayurvedic treatment	5

study were undecided about CAM. This highlights a sub-group of patients where targeted education on CAM could be helpful. While most CAM modalities were not directly harmful when used complementarily, we uncovered through this study several hazardous CAM interventions that were being used among our patient population. Understanding the alleged evidence and potential toxicities of these modalities allows us to be better placed to provide education and counsel about these therapies. We also discovered that almost half of respondents used more than one CAM intervention, raising the risk of adverse treatment interaction.

Healthcare professionals appear to be an important source of CAM information among respondents. This did not come as a complete surprise to us as there are several general practices in the Northland region that serve as integrative medicine hubs, promoting a wide range of CAM while delivering conventional therapies. Patients may also mistakenly attribute unregulated/unregistered CAM practitioners as healthcare professionals. In the light of potential toxicities, marketing scams, a kaleidoscope of modalities and an increasing number of quack practitioners, there is a need for more governmental regulation over the industry.

Word-of-mouth remains the main source of CAM information among respondents in this study. This highlights the importance of extending CAM education beyond patients to their family and wider community. However, the internet and social media are likely to become increasingly important, hence the need to channel adequate resources to develop evidence-based online resources for patient use. For instance, the Memorial Sloan Kettering Cancer Centre (MSKCC) website has an excellent integrative medicine section providing useful and evidence-based information on CAM.[17]

Perhaps the most practical step to address CAM use among patients with cancer is to foster open communication about CAM in day-to-day cancer care. Strategies to create a non-threatening environment is the first step. Simple measures such as placing information posters regarding CAM in waiting rooms, distributing information leaflets and incorporating a question regarding CAM during medication reviews can help create awareness and serve as conversation starters in the consultation or treatment floor. In fact, there is evidence that patients want their cancer-care professionals to provide them with evidence-based information on CAM.[18] Healthcare professionals who look after patients with cancer should receive training and guidance on how best to communicate effectively with patients regarding CAM. A systematic review conducted by Schofield et al. listed eight imperative steps, which include eliciting understanding, respecting ethnic and epistemological frameworks, active listening, being responsive to patients' emotional states and provide balanced evidence-based advice.[19] Discussions regarding CAM should not be limited to a patient's initial consultation appointment alone, but should be raised at critical junctures of a patient's treatment journey.

The Clinical Oncology Society of Australia (COSA) published a position paper regarding CAM in 2013, which listed some additional strategies that could be employed.[13] The position paper suggested categorising CAM into three categories (safe and beneficial, safe with uncertain benefits and potentially harmful) and having a reference table in consultation rooms to facilitate evidence-based recommendations regarding complementary medicine during patient encounters. Open communication with CAM providers was advocated. The statement also highlighted the need to inform patients of some of the consequences of CAM, which can include financial toxicity and exclusion from clinical trials. Lastly, keeping up to date with the latest CAM was suggested. Due to time constrains, selecting a champion (e.g., pharmacist/nurse) as a reference within a service who is resourced to stay abreast on CAM may be a more efficient way of achieving this.

There are several limitations to this study. Firstly, only the views of patients who were attending their assessment and treatment appointments were sampled, inadvertently excluding those who have chosen to terminate or end engagement with conventional healthcare services in favour of utilising alternative therapies. Hence, the prevalence of CAM use in the overall Northland population with a diagnosis of cancer is likely greater. Secondly, there are limitations inherent to the instrument employed. While we designed a simple questionnaire to facilitate self-administration, responses were open to inaccuracies due to issues such as language barriers, time constrains leading to rushed responses and misinterpretation of questions. The questionnaire did not distinguish between complementary only, alternative only or both complementary and alternative therapy users. Lastly, while patients' perspectives were sampled, this was by no means exhaustive, with the responses often raising more questions than answers. A qualitative study, such as one utilising patient interviews, would have been more appropriate for this purpose.

In conclusion, CAM use is common and will remain an important entity in day-to-day cancer care across oncology treatment centres nationwide. We demonstrated in this study the utility of local research into CAM, which serves to raise awareness about the landscape of CAM use in a specific patient population. This in turn facilitates training and planning among healthcare professionals to address CAM use among their patients.

COMPETING INTERESTS
None to disclose.

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Appendix

Jim Carney Cancer Treatment Centre

NORTHLAND DISTRICT HEALTH BOARD
Te Poari Hauora Ā Rohe O Te Tai Tokerau

Complementary and Alternative Medicine Study

Dear patients and whanau,

Complementary and Alternative Medicine (CAM) is a general term used to describe therapies that are typically not part of Conventional Western medicine. In other words, these are therapies that are usually not offered by your doctor. Conventional western medicine includes treatment such as surgery, chemotherapy, radiation therapy, and hormone therapy.

CAM has been used to treat a wide range of conditions including cancer. In this study, we hope to know how much our patients and their whanau, **know, use, think and feel about CAM** in the treatment of cancer.

This questionnaire is designed to preserve your confidentiality and your response will by no means affect the care we desire to give you. If you do not understand any of the questions, or require assistance to complete this survey, please let our receptionist or any of our nurses know.

Please tick the relevant boxes and insert the completed surveys into the designated box in the reception area.

Thank you so much for participating!

Section A

Please tick the relevant box

1) **I am** A patient ☐ Family/ friend of a patient ☐

2) **Gender**: Male ☐ Female ☐

3) **Ethnicity:** Maori ☐ NZ European ☐ Asian ☐ Pacific Islander ☐
Other Ethnicity: ☐ Please specify: _____

4) **Age (years):** <20 ☐ 21- 40 ☐ 41-60 ☐ 61-80 ☐ >81 ☐

Section B

Please answer this section **ONLY IF YOU ARE A PATIENT** receiving treatment for cancer. Kindly tick the relevant boxes (you can tick more than 1 box)

1) This list contains some of the most popular Complementary and Alternative therapies used in the treatment of cancer. Have you used or are you currently using any of these therapies?

Acupuncture /Chinese Medicine	☐	Ayurvedic Medicine	☐
Intravenous High Dose Vitamin C	☐	Maori Medicine	☐
Kangen Water (alkaline water)	☐	Homeopathy	☐
Miracle Mineral Solution	☐	Anti-cancer/detox diet	☐
Medical Cannabis	☐	Acupressure	☐
Ozone therapy	☐	Colonic irrigation	☐
Chelation therapy	☐	Gerson Therapy	☐
Vitamin B17 (Laetrile)	☐	Electromagnetic therapy	☐
Crystal therapy	☐	Naturopathic therapy	☐
Other therapies not listed here:	☐		

Kindly enter the name of the therapy not listed: _____

2) Where did you learn about these therapies?

Searching the internet	☐	Social Media		
My doctor/ healthcare professional	☐	Facebook ☐	Whatsapp ☐	
Newspaper/Books/Magazines	☐	Twitter ☐	Pinterest ☐	
Word of Mouth (friends/relatives)	☐	Youtube ☐	Instagram ☐	
Advertisements	☐	Reddit ☐	Google+ ☐	
Alternative medicine therapist	☐			

3) For the treatment of cancer, I

Have used/am currently using CAM	☐	Will not consider using CAM	☐
Undecided about whether to use CAM	☐	Intend to use CAM in the future	☐

4) If you have used or if you are currently using CAM, did you tell your oncologist/haematologist before starting? Yes ☐ No ☐

5) I will use CAM in cancer treatment:

Before using conventional western medicine	☐
Together with conventional western medicine	☐
If and when conventional western medicine fails	☐

Section C

Please tick the relevant box **(Only tick NA (not applicable) if the question is not relevant to you)**

	Agree	Neutral	Disagree	NA
I believe CAM therapies are based on strong scientific evidence in cancer treatment.				
I believe CAM can be effective in curing cancer				
I believe CAM can be effective in lessening the symptoms of cancer				
I have used CAM and it has been beneficial to me in my journey through cancer.				
I believe CAM promotes a more holistic view of health compared to conventional western medicine in cancer treatment.				
I believe CAM has less side effects compared to conventional western medicine				
I am aware that CAM therapies can be dangerous				
I believe CAM is natural, unlike conventional western medicine				
Using CAM helps me feel that I am in control of my cancer treatment				
The stories of those who successfully underwent CAM therapies for cancer encourages me to choose this treatment				
I am encouraged by my family and friends to use CAM in cancer treatment.				
I like the resources on the internet and media concerning CAM				
I believe most CAM advertisements are scams				
I use CAM because I trust my CAM provider (e.g. doctor/therapist/naturopath)				
I feel that CAM has a more positive message compared to conventional western medicine.				
I distrust conventional western medicine in cancer treatment because I believe it is heavily influenced by drug companies				
I trust my oncologist/ haematologist in advising me about CAM therapies in cancer treatment				

	Agree	Neutral	Disagree	NA
I feel uncomfortable talking to my oncologist/ haematologist about my use/ desire to use CAM in cancer treatment.				
I trust the public healthcare system to provide me with good cancer treatment and care				
I believe CAM should be funded by the government and integrated into the public healthcare system.				

End of Questionnaire

Thank you for your help.

Please remember to return this questionnaire to the reception.

Pharmacologic therapy among patients with type 2 diabetes mellitus admitted to the cardiology service

Evelyn Lesiawan, Thomas Seaton, Jocelyne Benatar, Jithendra B Somaratne

ABSTRACT

AIM: To review the management of diabetes control in patients with type 2 diabetes admitted to the cardiology service at Auckland City Hospital for over 48 hours; to assess how many would potentially benefit from introduction of empagliflozin under current Pharmac guidelines.

METHODS: A retrospective audit of all admissions into cardiology between 1 November 2020 and 31 January 2021 prior to the availability of empagliflozin. Data collected included diagnosis and presence of type 2 diabetes, HbA_{1c} and diabetes medications.

RESULTS: A total of 449 patients were admitted, of whom 98 had type 2 diabetes. The median age was 64 years old (IQR 56–76) and 66% of patients were male. Pacific peoples were over-represented in this study population. Fifty percent had an HbA_{1c}>60mnmol/mol and diabetes medication was changed in 50% of these. Overall, 50% of patients would be eligible for empagliflozin under current criteria.

CONCLUSIONS: High proportions of patients have poor glycaemic control and are not up-titrated, suggesting a missed opportunity for medication optimisation. Pacific peoples are over-represented in this group, suggesting that they are at high risk of diabetes and cardiovascular admissions. Empagliflozin provides a targeted way to address renal and cardiovascular outcomes.

Introduction

Type 2 diabetes mellitus (T2DM) is an important risk factor for cardiovascular disease. It confers a two- to four-fold increase in cardiovascular risk[1–3] and is associated with poor outcome. Intensive glycaemic control with agents such as sulphonylureas and insulin have little effect on cardiovascular outcomes and are associated with increased risk of hypoglycaemia.[4] Until February 2021, second-line agents in New Zealand were predominantly sulphonylureas and insulin. These drugs are associated with increased mortality,[5] so are not usually introduced or up-titrated during an acute cardiovascular admission unless HbA_{1c} levels are above 60mmol/mol. Vildagliptin was publicly funded in October 2018 but has limited effects on glycaemic control and offers no cardiovascular benefit.[5]

The advent of sodium-glucose co-transporter 2 (SGLT-2) inhibitors has changed the landscape in the management of T2DM. These drugs reduce all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction and progression of kidney disease without the risk of hypoglycaemia.[6–8] More recent studies indicate that these medications also have similar effects in those with heart failure or chronic kidney disease without diabetes.[8–9] These data strongly suggest these medications should be considered cardiovascular and renal therapy rather than purely agents to improve glycaemic control. A consensus guideline by the American Diabetes Association and the European Association for the Study of Diabetes recommends SGLT-2 inhibitors as second-line agents after metformin for the management of hyperglycaemia in patients with T2DM.[10]

Empagliflozin, an SGLT-2 inhibitor, was publicly funded in New Zealand on special authority from 1 February 2021 for those with T2DM who have an HbA_{1c}≥53mmol/L on at least one blood glucose lowering agent. To target those with T2DM who are most likely to benefit from these medications, Pharmac require certain enrichment criteria be met to qualify for subsidisation. For instance, prerequisites include established renal or cardiovascular complications of T2DM or an increased risk of future cardiovascular disease. The special authority criteria, for the first time, included ethnic groups at higher risk of complications such as Māori and Pacific people (Figure 1).[11]

The aims of this retrospective audit of patients admitted to an inpatient cardiology service are to: measure the prevalence of T2DM; describe their glycaemic control; assess changes to glycaemic treatment during the index hospitalisation; and

Figure 1: Criteria for subsidy of empagliflozin by special authority. Obtained from the New Zealand Formulary website.[11]

Initial Application

Applications from any relevant practitioner. Approvals valid without further renewal unless notified.

Pre-requisites

Patient has type 2 diabetes

and

Patient is Māori or any Pacific ethnicity **or**

Patient has pre-existing cardiovascular or risk equivalent (see note a) **or**

Patient has an absolute 5-year cardiovascular disease risk of 15% or greater according to a validated cardiovascular risk assessment calculator **or**

Patient has a high lifetime cardiovascular risk due to being diagnosed with type 2 diabetes during childhood or as a young adult **or**

Patient has diabetic kidney disease (see note b) **

and

Target HbA_{1c} (of 53mmol/mol or less) has not been achieved despite the regular use of at least one blood-glucose lowering agent (e.g. metformin, vildagliptin or insulin) for at least 3 months

determine the proportion that are eligible for empagliflozin.

Methods

All patients admitted to the cardiology service at Auckland City Hospital during the 3-month period between 1 November 2020 and 31 January 2021 are included in this retrospective study. Patients were identified by the Health Information and Technology Service at Auckland District Health Board. Any patient readmitted during this period was included in the analysis only once. The inclusion criteria were a diagnosis of T2DM and admission under the cardiology service for more than 48 hours. The diagnosis of T2DM was defined by a historical $HbA_{1c} \geq 50$mmol/mol[8] and documentation of physician diagnosis in the medical record. When a prior HbA_{1c} measurement was unavailable, a clinical diagnosis was deemed sufficient.

Chronic kidney disease was defined according to the position statement from Kidney Disease: Improving Global Outcomes (KDIGO).[12]

Stage 1 (>90mL/min/1.73m2), Stage 2 (60–89mL/min/1.73m2), Stage 3A (45–59mL/min/1.73m2), Stage 3B (30–44mL/min/1.73m2), Stage 4 (15–29mL/min/1.73m2), Stage 5 (<15mL/min/1.73m2).

Albuminuria was classified according to the urinary albumin:creatinine ratio. It was defined as minimal <3mg/g), mild (3 to 30mg/g), moderate (30 to 300mg/g) and severe (>300mg/g).[12] Optimisation of medication was defined as change in glycaemic medication at discharge. This was then stratified by patients with an HbA_{1c}>60mmol/mol, or an HbA_{1c}<60mmol/mol.

Two authors (EL and TS) obtained data through electronic medical records and clarified any discrepancies, if there were any, within the data. Information collected was stored on Excel and statistical analysis was done on this program. Data collected included baseline demographics, anthropometric measurement, microvascular complications of diabetes, discharge diagnosis, cardiac and glycaemic therapy on admission and discharge and baseline admission laboratory results.

The cardiovascular comorbidities listed were defined as patients with a previous or current clinical diagnosis based on their medical records. When left ventricular ejection fraction was described as "normal", "mildly impaired", "moderately impaired" or "severely impaired" without a numeric fraction, these were converted to 55%, 45%, 35% and 30% respectively for the purpose of statistical analysis. Likewise, an NT-proBNP of <6pmol/L was recorded as 3pmol/L. Determination of eligibility for subsidisation of empagliflozin was based on published Pharmac criteria[11] and an estimated glomerular filtration rate (eGFR) >30mL/min.

Statistical analysis

Absolute numbers are presented as N. For continuous variables, both the mean ± standard deviation and median with the interquartile range (IQR) have been presented in the tables.

Results

Of 1,290 patients admitted to the cardiology service at Auckland City Hospital between 1 November 2020 and 31 January 2021, 449 patients were in hospital for >48 hours and 98 (22%) patients had T2DM (Figure 2). The median length of stay was 102 (IQR 74–181) hours, or 4 days. The most common reason for hospitalisation was coronary heart disease (41%) followed by heart failure (22%).

The baseline demographics are presented in Table 1. The median age was 64 (IQR 56–76) years and 66% of patients were male. The ethnicities in this study do not reflect the demographics of Auckland, with Pacific people over-represented at 30% (compared to 11% in the community).[13] European and Asian people were under-represented at 30% vs 47% and 24% vs 34% respectively.[14]

The median HbA_{1c} was 60mmol/mol (IQR 52–71). In this cohort, many had cardiovascular comorbidities with approximately 40% previously diagnosed with coronary heart disease and 22% with heart failure. Eighty-seven percent had chronic kidney disease Stage ≥2 and 61% had albuminuria (Table 2). Diabetic retinopathy was documented in 35% of patients, and 19% had established peripheral neuropathy.

Overall, 37% of patients had their glycaemic medications changed during their admission (Table 3). Just over half of all patients had no change to their glycaemic therapy and 11% of patients were discharged with no glycaemic treatment. In patients with an HbA_{1c}≥60 mmol/mol, 50% had their glycaemic medications changed, 6% were discharged on no treatment and 44% had no change.

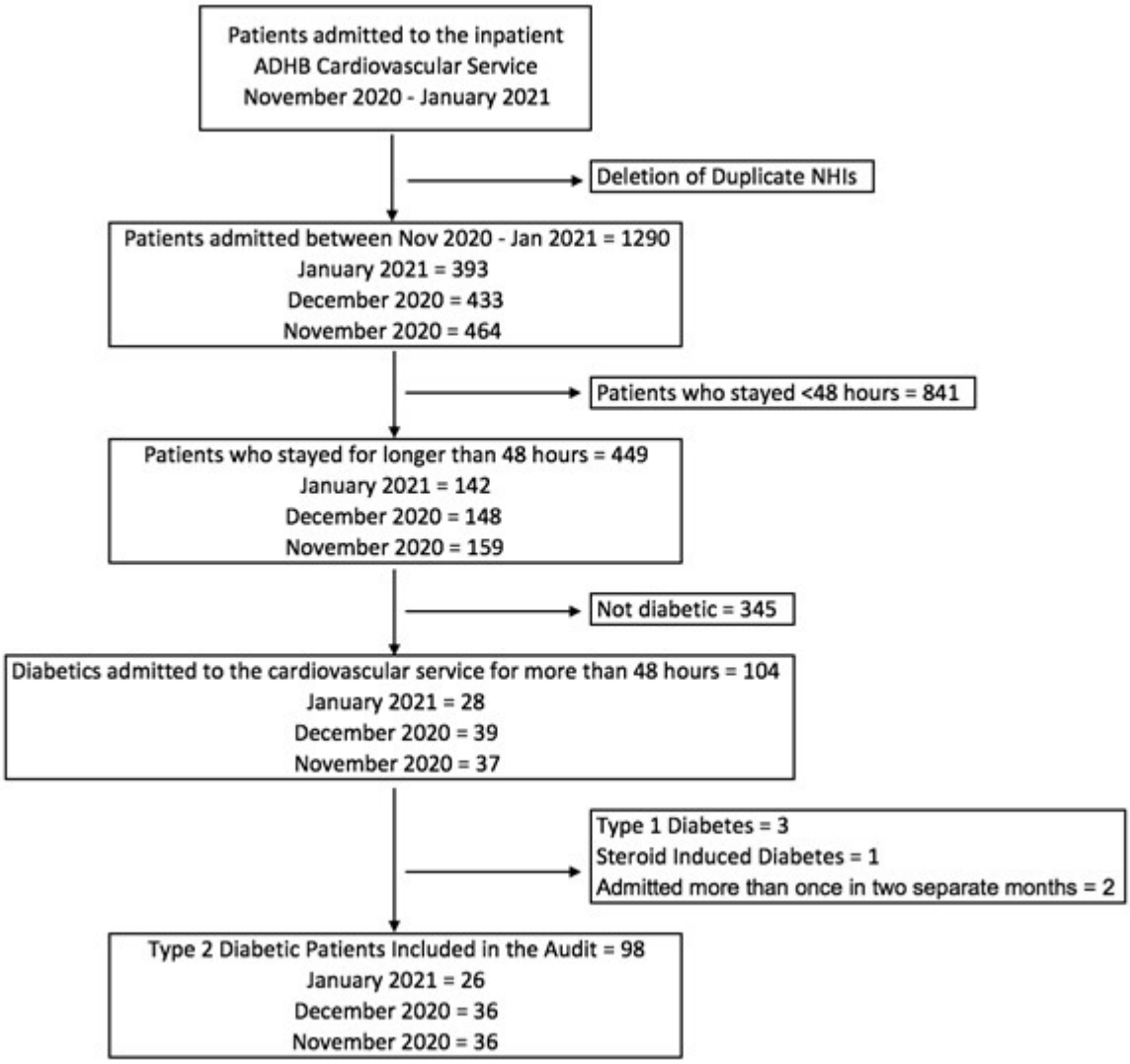
Of the 98 patients included in this study, 50% were eligible for subsidisation of empagliflozin using the current Pharmac special authority criteria (Table 4). Thirty-four patients (34%) did not meet the special authority criteria. Empagliflozin was contraindicated in 13% as their eGFR was less than 30mL/min. In comparison, only 34% of this cohort would meet the eligibility criteria for either of the two main randomised controlled trials that evaluated empagliflozin including EMPA-REG OUTCOME[7] and/or EMPEROR-REDUCED[9] (Table 4).

Common reasons for not meeting eligibility criteria for either study included: body mass index >45kg/m^2, eGFR<30mL/min/1.73m^2, HbA_{1c} less than 53mmol/mol or more than 85mmol/mol or if there were changes to their glycaemic medications within 12 weeks prior to admission. Five patients did not meet inclusion criteria due to their diagnosis being made within 3 months.

Discussion

In this contemporary single-centre retrospective study, we found that one in five patients under the cardiology service had T2DM. The prevalence of T2DM among cardiology inpatients is comparable to the rates seen nationally as per

Figure 2: Study flowchart.



the Acute Coronary Syndrome Quality Improvement (ANZACS-QI) registry data,[15] but perhaps lower than what is seen internationally where the prevalence of T2DM ranges from 30% to 40%.[16,17]

Overall, these patients had poor glycaemic control, with half of them having an HbA_{1c} of more than 60mmol/mol. Only half of those with poorer glycaemic control had any alteration of their glycaemic therapy during a hospitalisation under a cardiology service and 50% of this group met current Pharmac special authority criteria for subsidisation of empagliflozin. It is not clear why changes to glycaemic therapy are made infrequently in these inpatients. The two most likely reasons are a reluctance to change medications during a time of acute illness or pre-procedural fasting and a lack of prescribing confidence in relation to glycaemic pharmacotherapy. This may be exacerbated by the perceived risk of inducing hypoglycaemia with tight control on sulphonylureas and insulin, which is shown to have poor outcomes.

There are several ways in which the management of these patients could be improved during their cardiology hospitalisation. For instance, a diabetes screening tool pathway could be employed to identify more patients with poor glycaemic control. These patients are likely to benefit from the services of dedicated Clinical Nurse Specialists with specific training in both cardiology and diabetes. Alternatively, enabling cardiologists to alter medications themselves through further

Table 1: Baseline characteristics.

	Mean ± SD	Median (IQR)	N=98 (%)
Age [years]	65±13	64 (56–76)	
Male			65 (66)
Ethnicity			
European			29 (30)
Māori			15 (15)
Asian			24 (24)
Pasifika			29 (30)
Middle Eastern			1 (1.0)
Length of stay [hours]	153±131	102 (74–181)	
Presentation			
ST-elevation myocardial infarction			12 (12)
Non-ST-elevation myocardial infarction			16 (16)
Unstable angina			3 (3.1)
Heart failure			22 (22)
Arrhythmia			18 (18)
Aortic valve intervention			3 (3.1)
Non-cardiac chest pain			3 (3.1)
Other cardiac			6 (6.1)
Other non-cardiac			6 (6.1)
Body mass index [kg/m^2]	32±8.4	30 (25–37)	
Cardiovascular comorbidities			
Hypertension			77 (79)
Heart failure			48 (49)
Atrial arrhythmias			30 (31)
Coronary heart disease			68 (69)
Dyslipidaemia			61 (62)
Stroke			13 (13)
Peripheral vascular disease			5 (5.1)
Smoking status			
Never smoked			45 (46)

Table 1 continued: Baseline characteristics.

Ex-smoker			40 (41)
Current smoker			13 (13)
Cardiac medications			
Statins and/or ezetimibe			76 (78)
Alpha-blockers			11 (11)
Calcium channel blockers			25 (26)
ACEi or ARB			80 (82)
Beta-blockers			71 (72)
Diuretics			52 (53)
Left ventricular ejection fraction [%]	45±16	46 (33–58)	
NT-proBNP [pmol/L]	412±593	151 (42–551)	

Abbreviations: ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin II receptor blocker; IQR = interquartile range.

education would improve patients' care. Either of these options may help to overcome potential lack of prescribing confidence and break down siloed care. The significance of optimal management of T2DM in those with cardiovascular disease could be reflected and communicated more carefully on discharge summaries. Finally, among those admitted with acute coronary syndromes, HbA_{1c} could be made a mandatory field for data entry on the ANZACS-QI registry.[18] This would allow a more comprehensive study of glycaemic control in this important subset of patients admitted under cardiology services throughout the nation. Additionally, the inclusion and reporting of data relating to agents that improve cardiovascular outcomes, such as SGLT2 inhibitors and glucagon-like peptide 1 (GLP-1) agonists, would aid in the appropriate uptake of these medications.

Interestingly, half of those included in this study met the Pharmac special authority criteria for subsidisation of empagliflozin, while only one in three would have been eligible for enrolment in the two pivotal randomised controlled trials of empagliflozin. For the first time the Pharmac special authority criteria for subsidisation of a medication included ethnicities (Māori and Pacific people) at high risk of poor outcomes. The prevalence of T2DM is two to three times higher in these ethnic groups compared to others.[19] In our cohort, Pacific people were over-represented relative to the local population. Of those who met the special authority criteria, 47% were Māori or Pacific people. According to the current Pharmac criteria, those with an eGFR less than 30mL/min/1.73m^2 are ineligible for empagliflozin. However, it is known that empagliflozin can be safely used in those with chronic kidney disease who have an eGFR more than 20mL/min/1.73m^2.[9] A more recent analysis demonstrated the value of empagliflozin in improving renal and cardiovascular outcomes across the spectrum of chronic kidney disease.[20] Furthermore, it slows progression of kidney disease and reduces rates of renal events.[21]

Limitations

The sample size of this study is small and are all from a single centre. They may be non-representative of all patients admitted under a cardiology service throughout the country.

As this is a retrospective study, there were missing data in some variables. The short study timeframe of 3 months and the inclusion of a holiday period may introduce a temporal bias.

Table 2: Baseline diabetes characteristics.

	Mean (SD)	Median (IQR)	N=98 (%)
HbA_{1c} (mmol/mol)	64±18	59.5 (52–71)	
<60			48 (50)
≥60			48 (50)
Blood pressure			
SBP ≥140mmHg or DBP ≥90mmHg			25 (26)
SBP<140mmHg or DBP <90mmHg			73 (74)
eGFR [mL/min/1.73m^2]			
≥90			13 (13)
60 to <90			41 (42)
30 to <60			31 (32)
<30			13 (13)
Chronic kidney disease stage			
1			13 (13)
2			41 (42)
3A			20 (20)
3B			11 (11)
4			7 (7.1)
5			6 (6.1)
Urine albumin:creatinine ratio (mg/g)			
<3			34 (35)
≥3 to <30			43 (44)
≥30 to 300			11 (11)
>300			6 (6.1)
Nil			4 (4.1)
Glycaemic medications on admission			
Metformin			49 (50)
Vildagliptin			5 (5.0)
Vildagliptin/metformin combination			16 (16)
Sulphonylurea			18 (18)
Insulin			34 (35)
None			16 (16)

Abbreviations: DBP = diastolic blood pressure; eGFR = estimated glomerular filtration rate; IQR = interquartile range; NTproBNP = N-terminal pro-brain natriuretic peptide; SBP = systolic blood pressure.

Table 3: Changes to glycaemic medications during admission.

All patients (n=98)	
Changed	36 (37%)
No change	51 (52%)
No treatment at discharge	11 (11%)
HbA_{1c}>60 mmol/mol (n=48)	
Changed	24 (50%)
No change	21 (44%)
No treatment at discharge	3 (6.0%)
HbA_{1c}≤60 mmol/mol (n=48)	
Changed	12 (25%)
No change	8 (17%)
No treatment at discharge	28 (58%)

NB: Two patients had type 2 diabetes as part of their medical history, however, their primary residence was not Auckland, so no HbA_{1c} was recorded on their electronic medical records, thus they were not included in the sub-group analysis of HbA_{1c} control.

Table 4: Eligibility for subsidisation of SGLT-2 trials.

Eligible for subsidisation of empagliflozin under special authority	
Yes	49 (50%)
No due to <3 months glycaemic therapy prior to admission	11 (11%)
No due to HbA_{1c}≤53mmol/mol	23 (23%)
Insufficient information	2 (2.0%)
Excluded as eGFR<30 mL/min/1.73 m2	13 (13%)
Eligible for inclusion in EMPA-REG OUTCOME and/or EMPEROR-Reduced	
Yes	34 (35%)
No	64 (65%)

Abbreviations: eGFR = estimated glomerular filtration rate; EMPA-REG OUTCOME = Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes; EMPEROR-Reduced = Cardiovascular and Renal Outcomes with Empagliflozin in Heart Failure.

Conclusion

In this 3-month retrospective snapshot study on this single centre, we found a high prevalence of T2DM among patients admitted under the cardiology service. These patients generally had poor control. Most did not have any change to their glycaemic therapy. Patients with established cardiac disease constitute a high-risk population that warrant opportunistic optimisation of their diabetes therapy during their hospitalisation. With the recent subsidisation of SGLT2 inhibitors and GLP-1 agonists, glycaemic agents that improve cardiovascular outcomes, cardiology services throughout the country should be comfortable with the initiation and titration of these medications. Moreover, each hospitalisation should be viewed as an opportunity to initiate these medications where appropriate.

COMPETING INTERESTS
None to declare.

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The incidence of symptomatic venous thromboembolism following orthopaedic surgery at Bay of Plenty District Health Board

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ABSTRACT

AIM: To investigate the incidence of symptomatic venous thromboembolism (VTE) after orthopaedic surgery.

METHOD: We performed a retrospective cohort study investigating the incidence of symptomatic VTE within 90 days of orthopaedic surgery in the Bay of Plenty District Health Board (DHB). Risk factors and antithrombotic regimens were also reviewed.

RESULTS: After 1,133 unilateral total hip joint replacements (THJRs), there were six VTEs (incidence 0.5%, 95% CI 0.2–1.1%), four deep vein thromboses (DVT) (0.4%, 0.1–0.9%) and three pulmonary emboli (PE) (0.3%, 0.1–0.8%). Following 898 unilateral total knee joint replacements (TKJRs), 18 patients developed VTEs (2.0%, 1.2–2.9%), five developed DVTs (0.6%, 0.2–1.3%) and 16 developed PEs (1.8%, 1.1–2.9%). There were five VTEs after 224 THJR revisions (2.2%, 1.0–5.1%), five VTEs after 110 TKJR revisions (4.5%, 2.0–10.2%) and 16 VTEs after 846 hip fracture surgeries (1.9%, 1.2–3.0%). VTE risk factors were ICU admission post operatively and having known coronary or cerebrovascular disease. Within 1 week of surgery, 38.5% (30/78) of VTEs were diagnosed and within 2 weeks 66.7% (52/78) were diagnosed. Aspirin was being taken by 44% (34/78) of VTE patients and 26% (19/78) were on more potent antithrombotics.

CONCLUSION: VTE is a rare complication of orthopaedic surgery. The highest risk period is the initial 2 weeks after a procedure. VTE can develop despite pharmacological thromboprophylaxis.

Deep vein thrombosis (DVT) and pulmonary embolism (PE), collectively known as venous thromboembolism (VTE), are significant potential post-operative complications.[1] Prevention of VTE is important because 20–50% of patients with symptomatic DVTs develop post-thrombotic syndrome, and 5.4–14.6% of in-hospital deaths are caused or contributed to by PEs.[2–6] As antithrombotic agents significantly increase the likelihood of bleeding, risk stratification must be employed to target those with a favourable risk-to-benefit ratio.[7–9] While numerous risk factors are involved in the pathogenesis of VTE, a significant one is major orthopaedic surgery. In the absence of pharmacological thromboprophylaxis, the incidence of symptomatic VTE after total hip joint replacement (THJR), total knee joint replacement (TKJR) and hip fracture surgery is 4.3%.[10]

Effective strategies to reduce the incidence of post-operative VTE include pharmacological and mechanical prophylaxis in the form of intermittent pneumatic compression and early mobilisation. A systematic review, published in *JAMA*, of 47 studies involving 44,844 patients taking pharmacological prophylaxis found the incidence of symptomatic VTE following hip or knee joint arthroplasty prior to discharge was 0.53% and 1.09% respectively.[11] Their incidence of DVTs was 0.26% and PEs 0.14% following hip arthroplasty, and 0.63% and 0.27% after knee arthroplasty. Meta-analysis of 27 studies from Kwok et al. found intermittent pneumatic compression reduced the incidence of DVT by 59% and PE by 58% for elective orthopaedic patients.[12]

With these advances in thromboprophylaxis, the incidence of VTE following orthopaedic surgeries is relatively low. Shahi et al. analysed 173,591 revision arthroplasties and found the incidence of VTE, DVT and PE following revision of THJR to be 1.34%, 1.06% and 0.37%, and for revision of TKJR 1.16%, 0.88% and 0.34%.[13] McNamara et al. analysed 5,300 patients admitted for neck of femur (NOF) fractures and found their incidence for VTE within 1 year of admission was 2.2%, DVTs was 1.5% and PEs 0.7%.[14] The incidence of VTE was highest following intramedullary nailing at 3.3%, followed by sliding hip screw at 2.9%, hemiarthroplasty at 1.7%, multiple screws at 1.6%, then non-surgical treatment at 1.1%. More locally

in New Zealand, Dixon et al. reviewed 5,046 procedures performed in at Waitematā District Health Board (DHB) and found the incidence of VTE in the 90 days following total hip joint replacement to be 1.5%, knee joint replacement 5.3% and NOF fracture surgery 4.2%.[15] Lapidus et al. investigated the incidence of VTE in the 6 weeks following 45,968 orthopaedic procedures. They found the incidence of VTE was 12% following internal fixation of pelvic fractures, 3.6% after ankle fractures internal fixation, 0.3% after spinal surgeries and 0.4% after upper limb surgeries.[16]

The incidence of VTE following orthopaedic surgery in Tauranga, New Zealand is currently unknown. This study aims to investigate the incidence of VTE in Tauranga Public Hospital following various orthopaedic procedures. Secondary aims are to investigate the relative risk of VTE risk factors in our cohort and the time from operation to VTE diagnosis.

Method

All patients undergoing orthopaedic surgery at Tauranga Public Hospital admitted in a 5-year period (31 July 2016 to 1 August 2011) were identified from hospital discharge data. Patients discharged from orthopaedics who were treated non-operatively were excluded. Patients who were managed operatively routinely used Thrombo-Embolus Deterrent (TED) stockings and mechanical prophylaxis in the form of calf compression or foot pumps. Arthroplasty patients typically mobilised the day after surgery.

Patients diagnosed with symptomatic VTE at Tauranga Public Hospital from 1 August 2011–29 October 2016 were identified by ICD coding (I26.0, I26.9, I74.3, I74.9, I80.2, I80.3, I82.8, I82.9, I97.8, T81.7, T85.86). Private radiology clinics performing compression ultrasounds in Tauranga were contacted for a list of National Health Indexes (NHIs) of patients diagnosed with DVTs within the same timeframe. These NHIs were crossmatched with the list of patients who had undergone orthopaedic surgeries. These notes were then formally reviewed to ensure they had a DVT diagnosed by ultrasound, or PE diagnosed by CT pulmonary angiogram (CTPA) within 90 days after their orthopaedic surgery. If the VTE was diagnosed within 90 days of multiple procedures, the most recent lower limb joint arthroplasty or revision arthroplasty was considered causative.

Incidence and prevalence data were analysed using Wilson's score method assuming a binomial distribution. Risk ratios were calculated using the Wald test with a small sample adjustment and bootstrap method. Risk ratios were calculated comparing the prevalence of risk factors in all surgical patients to VTE patients. Additionally, these were calculated comparing all hip and knee arthroplasty and revision arthroplasty patients to those undergoing the same procedures who developed VTE. These were calculated using the statistical software "R" using the prop.test function without Yates' continuity correction and the risk.ratio command, respectively.[17]

Results

Table 1 summarises the basic characteristics of subjects included in this study. Over the 5-year period, 11,394 orthopaedic procedures were performed on 9,328 patients, 78 of whom developed VTE. 48.4% of patients were female, while 54.8% of VTE patients were female. 42.9% of surgical patients and 67.9% of VTE patients were 65 years old or older. Most patients were of European descent.

The incidence of symptomatic VTE within 90 days of their respective procedures is summarised in Table 2 and Figure 1. The incidence of VTE following TKJRs and revision of TKJRs was higher than their THJRs counterparts, although this difference was only statically significant for unilateral primary arthroplasties. For NOF fracture surgeries, intramedullary nails had the highest incidence of VTE, followed by hip hemiarthroplasty, cannulated screws and dynamic hip screws, although these differences did not reach statistical significance. The incidence of VTE following ankle fracture surgeries are comparable to that of lower limb total joint arthroplasties. The operations associated with the lowest incidence of VTE were spinal, upper limb and paediatric surgeries.

Table 2 summarises the relative risk of various risk factors. Risk factors for VTE include advanced age, comorbid cardiovascular disease and being admitted to the intensive care unit post operatively. Only the latter two were statistically significant risk factors for VTE in lower limb arthroplasty and revision arthroplasty patients.

The time from the most recent orthopaedic procedure to the diagnosis of VTE is illustrated in Figure 2. Thirty-eight point five percent of VTE were diagnosed within 1 week of the patients' operations, 66.7% within 2 weeks and 75.6% within 3 weeks.

The medication charts were available for 70

Table 1: Basic patient demographics.

	All orthopaedic patients N=11,394 (%)	**VTE patients N=84 (%)**
Total procedures	11,394	84
Total patients	9,328	78
Elective procedure	5,674 (49.8)	41 (48.8)
Age ≥65	4,884 (42.9)	57 (67.9)
Female	5,514 (48.4)	46 (54.8)
Māori	1,574 (13.8)	6 (7.7)
Pacific Islander	148 (1.3)	2 (2.4)
European	9,420 (82.7)	73 (86.9)

(89.7%) of VTE patients in this study. Table 4 shows the proportion of these patients on each pharmacological thromboprophylactic agent at the time of VTE diagnosis. At least 67.9% of patients were on pharmacological thromboprophylaxis, 43.6% of whom were taking aspirin monotherapy, and the remaining 24.4% were on more potent antithrombotics. We did not have access to the thromboprophylactic regimens of patients who did not develop VTE.

Discussion

These results show that VTE are relatively rare complications of orthopaedic surgery at Tauranga Hospital. The highest rates were seen in those undergoing total lower limb arthroplasty, revision of lower limb arthroplasty, NOF and ankle fracture surgery. Surprisingly, more patients were diagnosed with PEs than DVTs. We identified comorbid cardiovascular disease and being transferred to ICU post operatively as risk factors for VTE. The majority of VTEs were diagnosed within 1 month of surgery. At the time of VTE diagnosis, almost half of these patients were taking aspirin and over a quarter were on more potent antithrombotic regimens. This highlights that using anticoagulants cannot eliminate the risk of post-operative VTE.

The rates of VTE following lower limb joint arthroplasty and revision arthroplasty in this study are higher than the rates reported in other studies.[11,13] However, it is important to note that these studies analysed VTE developing from surgery to discharge, while our rates are within 90 days of surgery. Employing their methodology excludes 52% of our VTE cases. Another major difference between our study and this meta-analysis is that they only included patients receiving pharmacological thromboprophylaxis. Not all patients in this study received anticoagulants due to contraindications and clinical judgement. The decision to prescribe pharmacological thromboprophylaxis is not always straightforward, as demonstrated by two of our patients who developed haemarthrosis following TKJR, prompting cessation of anticoagulants—then they subsequently developed PEs. Another factor contributing to our higher incidence of VTE was that five of our patients also underwent non-orthopaedic surgery within 90 days of their VTE diagnosis, which likely contributed to its development. A study from New Zealand with similar methods had results comparable to ours, with a VTE incidence of 1.5% following hip joint arthroplasty and 5.3% following knee joint replacement.[15]

One weakness of this study is not having data on the thromboprophylactic regimens of patients who did not develop VTE. Consequently, we were unable to determine what antithrombotic agent was most effective. Another weakness is our

Table 2: The number of procedures performed and the incidence of symptomatic VTE.

Operation	Number performed	Number of VTEs (incidence, 95% CI)	Number of DVTs (incidence, 95% CI)	Number of PEs (incidence, 95% CI)
All orthopaedic procedures	11,398	78 (0.7, 0.5–0.9)	32 (0.3, 0.2–0.4)	50 (0.4, 0.3–0.6)
All lower limb total joint replacements and revision of total joint replacements	2,396	35 (1.5, 1.1–2.0)	13 (0.5, 0.3–0.9)	26 (1.1, 0.7–1.6)
Unilateral THJR	1,133	6 (0.5, 0.2–1.1)	4 (0.4, 0.1–0.9)	3 (0.3, 0.1–0.8)
Bilateral THJR	6	0	0	0
Revision of THJR	224	5 (2.2, 1.0–5.1)	1 (0.4, 0.1–2.5)	4 (1.8, 0.7–4.5)
Unilateral TKJR	898	18 (2.0, 1.2–2.9)	5 (0.6, 0.2–1.3)	16 (1.8, 1.1–2.9)
Bilateral TKJR	25	1 (4.0, 0.1–19.5)	0	1 (4.0, 0.1–19.5)
Revision of TKJR	110	5 (4.5, 2.0–10.2)	3 (2.7, 0.9–7.7)	2 (1.8, 0.5–6.4)
Hip fracture surgery	846	16 (1.9, 1.2–3.0)	6 (0.7, 0.3–1.5)	10 (1.2, 0.6–2.2)
Dynamic hip screw	348	4 (1.1, 0.3–2.9)	3 (0.9, 0.3–2.5)	1 (0.3, 0.1–1.6)
Hip hemiarthroplasty	301	7 (2.3, 1.1–4.7)	2 (0.7, 0.2–2.4)	5 (1.7, 0.7–3.8)
Cannulated screws	99	2 (2.0, 0.6–7.1)	0	2 (2.0, 0.6–7.1)
Intramedullary nail	98	3 (3.1, 1.0–8.6)	1 (1.0, 0.2–5.6)	2 (2.0, 0.6–7.1)
Ankle fracture surgery	374	6 (1.6, 0.7–3.5)	2 (0.5, 0.1–1.9)	4 (1.1, 0.4–2.7)
Elective foot surgery	236	2 (0.8, 0.2–3.0)	1 (0.4, 0.1–2.4)	1 (0.4, 0.1–2.4)
Elective spinal surgery	349	2 (0.6, 0.2–2.1)	0	2 (0.6, 0.2–2.1)
Acute spinal surgery	89	0	0	0
Pelvic fracture surgery	48	0	0	0
Elective upper limb surgery	1,079	1 (0.1, 0–0.5)	0	1 (0.1, 0–0.5)
Acute upper limb surgery	1,185	0	0	0
Elective paediatric surgery	447	0	0	0
Acute paediatric surgery	725	1 (0.1. 0–0.8)	1 (0.1. 0–0.8)	0

Figure 1: The incidence of symptomatic VTE following orthopaedic surgery.

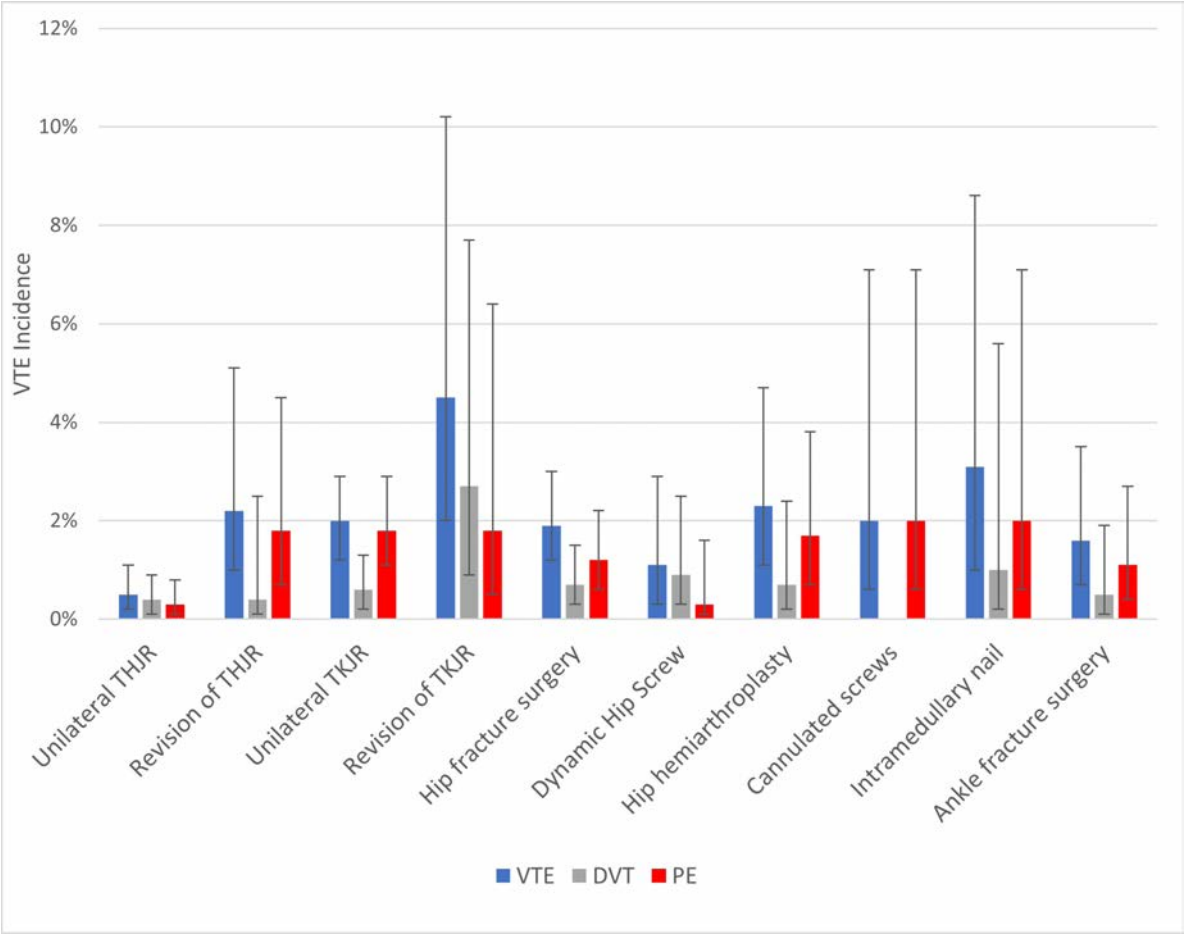

Figure 2: The time from surgery to VTE diagnosis.

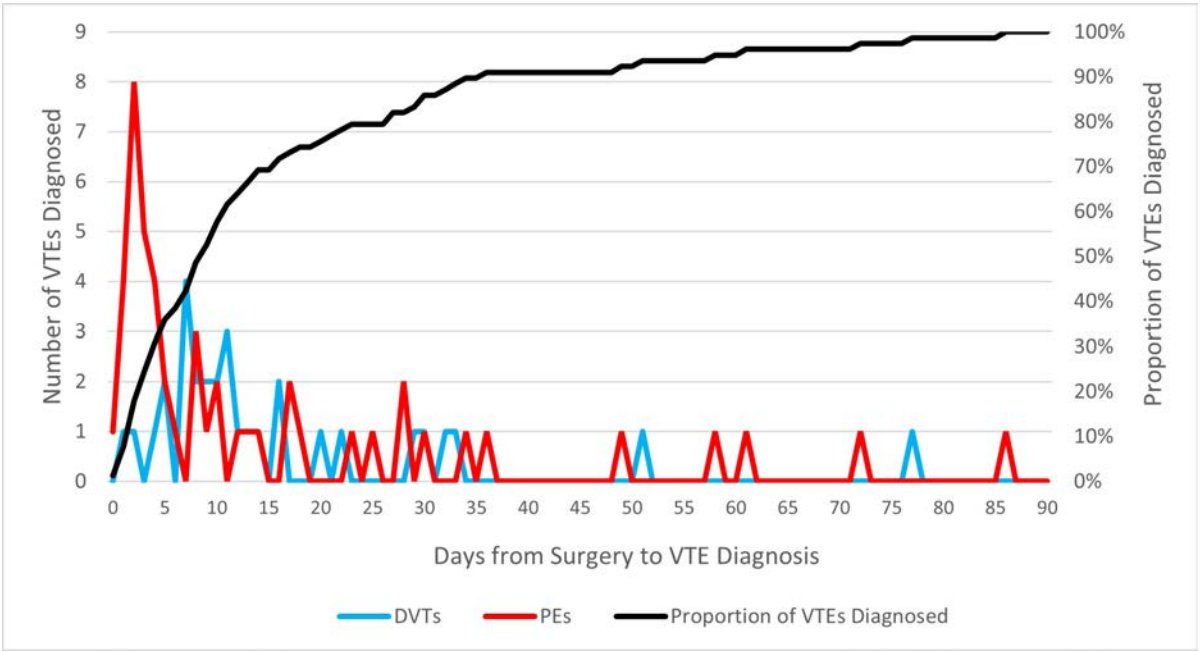

Table 3: The prevalence of risk factors for VTE among orthopaedic patients.

Risk factor	Surgical patients N (n=9,238)	VTE patients N (n=78), relative risk (95% CI)	Lower limb joint total arthroplasty and revision arthroplasty patients N (n=2,064)	Lower limb arthroplasty and revision arthroplasty VTE patients N (n=35), relative risk (95% CI)
Age ≥65	3,918 (42.0)	52 (66.7) (1.6, 1.4–1.9)	1,522 (73.8)	26 (74.3) 1.0 (0.8–1.2)
Female	4,465 (47.9)	45 (57.7) (1.2, 1.0–1.5)	1,118 (54.2)	20 (57.1) 1.1 (0.8–1.4)
Māori or Pacific Islander	1,459 (15.6)	8 (10.3) (0.7, 0.3–1.3)	193 (9.4)	3 (8.6) 0.9 (0.3–2.7)
Admitted to ICU post operatively	335 (3.6)	16 (20.5) (5.7, 3.6–9.0)	118 (5.7)	7 (20.0) 3.5 (1.8–6.9)
Known coronary heart disease or cerebrovascular disease	840 (9.0)	39 (50.0) (5.5, 4.4–7.0)	280 (13.6)	20 (57.1) 4 (3.1–5.7)
Diabetes	547 (5.9)	4 (5.1) (0.9, 0.3–2.3)	189 (9.2)	2 (5.7) 0.6 (0.2–2.4)
Current or ex-smoker	2,118 (26.1)	18 (23.1) (0.9, 0.6–1.4)	456 (23.3)	9 (25.7) 1.2 (0.7–2.1)
In residential care	246 (2.6)	1 (1.3) (0.5, 0.1–3.4)	15 (0.7)	0 (0)

sparse number of bilateral lower limb arthroplasty cases. Consequently, we cannot determine whether these patients are at higher risk than those undergoing unilateral arthroplasty. Additionally, this study is at risk of type II error due to small event numbers. Finally, we relied on hospital coding to identify patients diagnosed with venous thromboembolism. This may have failed to identify some cases. A major strength of this study is its high capture incidence. In Tauranga, CTPA is only performed at Tauranga Public Hospital, so all patients diagnosed with PE in Tauranga will be included in our data. While ultrasounds can also be performed at eight private radiology clinics in Tauranga, six were able to provide us with data, identifying six more DVT patients. Another plausible explanation as to why more PEs were diagnosed than DVTs is that the former carries a higher incidence of morbidity and mortality, therefore in patients with signs of both diseases,

Table 4: The pharmacological thromboprophylaxis agent of VTE patients

Thromboprophylaxis agent	Number of patients N=78 (%)
Aspirin	34 (43.6)
Clopidogrel	1 (1.3)
Enoxaparin	5 (6.4)
Rivaroxaban	6 (7.7)
Warfarin	3 (3.8)
Dabigatran	1 (1.3)
Aspirin and warfarin	2 (2.6)
Aspirin and rivaroxaban	1 (1.3)
None	17 (21.8)
Unknown	8 (10.3)

clinicians may opt to investigate for PEs first. Because the management of patients with PE does not change if they have a DVT, PE patients were less likely to be investigated for concurrent DVT. There is also evidence that PEs can occur in the absence of DVTs.[18]

This study highlights those with the greatest risk of post-operative VTE. Patients undergoing major lower limb surgery with comorbid cardiovascular disease and those requiring ICU admission post operatively have the greatest to gain from thromboprophylaxis. This suggests that the use of more potent anticoagulation for these patients may be appropriate, especially in the first 2 to 4 weeks after their procedure. In future research we plan to investigate the sequelae of VTEs in orthopaedic patients.

COMPETING INTERESTS
Joshua Read received a 12-week summer student scholarship to do a non-specified project. Mr Muir, Mr Vane and Dr Stringfellow received no financial support for this project.

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Longitudinal trends in community antibiotic consumption in the Waitaha Canterbury Region of Aotearoa New Zealand over 10 years (2012–2021): an observational study

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ABSTRACT

AIMS: To investigate community antibiotic consumption in the Waitaha Canterbury Region of Aotearoa New Zealand across 2012–2021.

METHODS: This observational study was based on antibiotic dispensing data from Waitaha Canterbury. Outcome measures included number of dispensings/1,000 inhabitants per year and defined daily doses/1,000 inhabitants per day (DIDs), expressed as average annual change (AAC). We stratified antibiotic dispensing per antibiotic group, and per the World Health Organization (WHO) AWaRE (Access, Watch, Reserve) classification.

RESULTS: Across 2012–2021, antibiotic dispensing decreased from 867 to 601 dispensings/1,000 inhabitants (AAC -4.2% [95%CI -4.3 to -4.2]). In the pre-COVID period of 2012 to 2019, antibiotic dispensings decreased with AAC of -3.5% (95%CI -3.6 to -3.5). Considering number of dispensings, the largest reductions were observed in quinolones (-14.6%), macrolides/lincosamides (-8.5%) and penicillins with extended spectrum (-4.8%). The number of dispensings increased for nitrofurans (6.0%) and first generation cephalosporins (28.1%), of which 98% comprised cefalexin dispensing. The proportion of Watch antibiotics decreased from 22.0% to 11.9%.

CONCLUSIONS: Community antibiotic consumption decreased in Waitaha Canterbury Aotearoa New Zealand from 2012 to 2021, as did use of Watch antibiotics. These changes concord with increasing antimicrobial stewardship guidance for more judicious use of antibiotics. Further research should investigate the factors driving the observed 10-fold rise in cefalexin dispensing.

Antimicrobial resistance is listed by the Health Emergency Preparedness and Response Authority among the top three health threats facing the European Union.[1] Worldwide, antibiotic resistant bacteria were associated with approximately 5 million deaths in 2019, and were the direct cause of death in 1.27 million cases.[2] One of the main drivers for antimicrobial resistance is overall antibiotic consumption in the community.[3] Insight into local antibiotic dispensing patterns in the community, where most antibiotics are used, is crucial to define areas of improvement. These include ensuring antimicrobial medicines are used optimally to treat infections while avoiding the harms associated with their use including antimicrobial resistance and adverse effects.[4]

In Aotearoa New Zealand, community care accounts for up to 95% of antibiotic dispensing.[5] Compared to other high-income countries, dispensing rates in Aotearoa New Zealand were the fourth highest, exceeded only by Greece, Italy and Korea in 2019.[6–8] Although community antibiotic dispensing decreased by 3.5% per year between 2015 and 2018 in Aotearoa New Zealand, it was still notably higher than in other high-income countries (i.e., ~4 defined daily doses per 1,000 inhabitants per day [DIDs]). Moreover, within Aotearoa New Zealand large variation exists in community antibiotic dispensing rates across regions ranging from 20 to 30 DIDs.[9] Compared to other regions in Aotearoa New Zealand, the Waitaha Canterbury Region had one of the lowest rates of people who are dispensed at least one systemic antibiotic per year in 2018.[10]

The World Health Organization (WHO) developed the AWaRe classification (Access, Watch, Reserve), which is designed for antimicrobial stewardship and surveillance purposes, and also enables international comparison.[11] The WHO defines Access antibiotics as antibiotics of choice for the most common infections whilst Watch

antibiotics are only recommended for specific indications (e.g., macrolides, quinolones, and second/third generation cephalosporins). The WHO AWaRe guideline recommends that >60% of antibiotic dispensings are Access antibiotics in the hospital and in the community.[12] Aotearoa New Zealand reached that target between 2000 and 2015, with 80% of all antibiotic dispensings in 2015 being from the Access classification, although AWaRE data for only the community setting has not yet been reported.

Studies in other high-income countries have shown recent decreases in total community use of antibiotics, and a change in antibiotic type.[13–15] Insight into local prescribing patterns and the relation to antibiotic guidance is essential to inform areas of improvement for antimicrobial stewardship programs. In this study, we aimed to investigate longitudinal trends in community antibiotic consumption in the Waitaha Canterbury Region of Aotearoa New Zealand between 2012–2021.

Methods

Ethics

This research was approved by the Human Ethics Committee of the University of Otago (HD22/032).

Study design and data collection

This was an observational study based on routinely collected data on systemic antibiotic prescriptions dispensed in the community from the National Pharmaceutical Collection in Aotearoa New Zealand.[16] We extracted data on all subsidised dispensed systemic antibacterial agents in the Waitaha Canterbury Region from 1 January 2012 to 31 December 2021. The dataset did not include antibiotics supplied to patients unsubsidised nor those supplied to prescribers for use in emergencies, for demonstration purposes, or for when an individual prescription is not practical (termed practitioner supply order). In 2021, Waitaha Canterbury covered 586,400 inhabitants, which comprised 12% of the total Aotearoa New Zealand population. In Waitaha Canterbury, 10% of inhabitants is of Māori ethnicity, 3% of Pacific ethnicity, 11% of Asian ethnicity, and 76% of Other ethnicity, which includes NZ European, Middle Eastern, Latin American and African, and others. Collected data included type of antibacterial agent, dosage and quantity dispensed. Antibiotic agents were grouped by Anatomic Therapeutic Chemical classification (see Appendix 1).[17] This grouping includes beta-lactamase sensitive penicillins, beta-lactamase resistant penicillins, penicillins with extended spectrum, combinations of penicillins including beta-lactamase inhibitors, macrolides/lincosamides, first generation cephalosporins, second generation cephalosporins, third generation cephalosporin, trimethoprim and sulphonamides, nitrofurans, quinolones, imidazoles, and other antibiotics. We stratified data per age group (<5 years, 5–9 years, 10–19 years, 20–59 years, ≥60 years)[9] and per prioritised ethnicity (Māori, Pacific people, Asian, and "Other", which included NZ European, Middle Eastern, Latin American and African, and others).[18] Statistics New Zealand prepared a custom dataset for the Aotearoa New Zealand Ministry of Health | Manatū Hauora, consisting of population projections stratified by district health board, age, sex and prioritised ethnicity. Projections were based on the 2013 census and updated in 2018.

Outcome measures

We assessed antibiotic consumption using different measures:[15] (i) number of dispensed prescriptions per 1,000 inhabitants per year, and (ii) defined daily doses per 1,000 inhabitants per day (DIDs). The defined daily dose is the assumed average maintenance dose per day for an individual drug in adults.[17]

Data analysis

First, we assessed total systemic antibiotic dispensing and performed regression analyses to assess trends over time (Poisson regression for number of dispensings, linear regression for DIDs). Because the infectious disease burden and antibiotic prescriptions decreased during the COVID-19 pandemic,[19] we analysed the period before the COVID-19 pandemic (2012 to 2019) separately. Second, we evaluated antibiotic dispensing per antibiotic group, and per the WHO AWaRE classification (see Appendix 1).[11] The WHO defines Access antibiotics as antibiotics of choice for the most common infections, whilst Watch antibiotics are only recommended for specific indications (e.g., macrolides, quinolones, and second/third generation cephalosporins). Third, we performed stratified analyses for age and ethnicity. Dispensed prescriptions with missing data for age (~6%) or ethnicity (~9%) were excluded for this analysis. All analyses were performed in R version v4.2.

Results

Overall antibiotic dispensing

Across the 10 years of the study, community antibiotic dispensing decreased by 30.7% (867 dispensings per 1,000 inhabitants per year in 2012 to 601 dispensings per 1,000 inhabitants per year in 2021) representing an average annual change (AAC) of -4.2% (95% CI -4.3 to -4.2)) (see Table 1). Furthermore, DIDs decreased by 20.8% (22.8 in 2012 to 18.0 in 2021), representing an AAC of -0.64 DIDs (95%CI -0.76 to -0.53)).

The largest reduction of antibiotic dispensing was observed in 2020 compared to 2019 (-108 dispensings per 1,000 inhabitants; -2.0 DIDs). Dispensings increased again in 2021, yet levels in 2021 were lower than in 2019.

In the stratified analysis focussing on the years 2012 to 2019, similar trends were observed in overall antibiotic dispensing (number of dispensings per 1,000 inhabitants: AAC -3.5% (95%CI -3.6 to -3.5), DIDs: AAC -0.64 DIDs (95%CI -0.75 to -0.53)), although differences were smaller.

Antibiotic dispensing per antibiotic group

Over the decade, the number of dispensings decreased in 10 of the 14 antibiotic groups (Figure 1; Appendix 2). The largest reductions in total number of dispensings were observed in macrolides/lincosamides (124 to 54 dispensings per 1,000 inhabitants; AAC -8.4% [95%CI -8.5 to -8.3]), penicillins with extended spectrum (201 to 139 dispensings per 1,000 inhabitants; AAC -4.8% [95%CI -4.9 to -4.8]), and combinations of penicillins with beta-lactamase inhibitors (134 to 91 dispensings per 1000 inhabitants; AAC -4.5% [95%CI -4.6 to -4.4]). The largest reduction in percentage was observed in quinolones (AAC -14.6% [95% CI -14.8 to -14.5]; 49 to 11 dispensings per 1,000 inhabitants). Increases in dispensings were observed for first-generation cephalosporins (3.4 to 38 dispensings per 1,000 inhabitants; AAC: 28.1% [95%CI 27.7 to 28.4]) and nitrofurans (19 to 34 dispensings per 1,000 inhabitants; AAC: 6.0% [95%CI 5.8 to 6.2]). The large increase in first generation cephalosporins was mainly attributable to increased dispensing of cefalexin (98%). In addition, increases for third generation cephalosporin and other antibiotics were observed, although absolute number of dispensings were low in these groups. The stratified analysis for 2012 to 2019 showed similar results (presented in Appendix 2).

When measured by DIDs, similar trends were observed for community antibiotic consumption with decreases in macrolides/lincosamides, combinations of penicillins with beta-lactamase inhibitors and penicillins with extended spectrum (Appendix 2). The largest reduction was, however, observed in tetracyclines (7.6 to 6.3 DIDs, AAC -0.20 DIDs [95%CI -0.25 to -0.16]). Similarly, increases were observed in first generation cephalosporins, nitrofurans, third generation cephalosporin and other antibiotics.

Table 1: Community antibiotic dispensings in Waitaha Canterbury in 2012–2021.

Year	Number of dispensings per 1,000 inhabitants per year	Defined daily doses per 1,000 inhabitants per day (DIDs)
2012	867	22.8
2013	833	22.5
2014	820	22.3
2015	781	21.2
2016	736	20.1
2017	733	19.8
2018	692	18.8
2019	681	18.9
2020	573	16.9
2021	601	18.0

Figure 1: Antibiotic dispensing per antibiotic group in Waitaha Canterbury in 2012–2021.

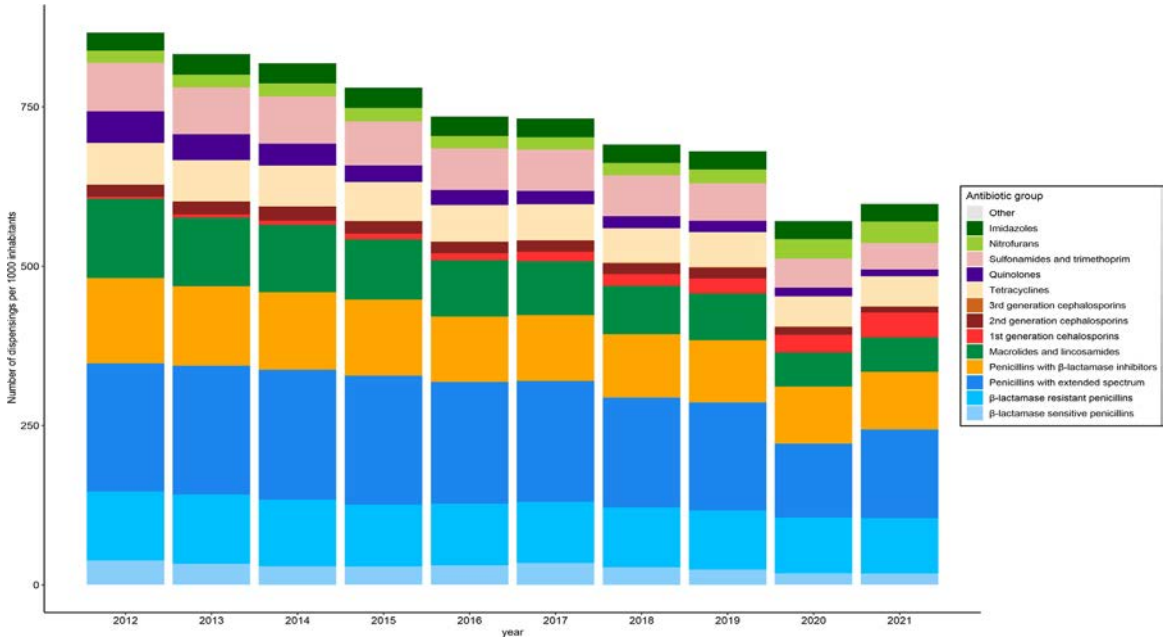
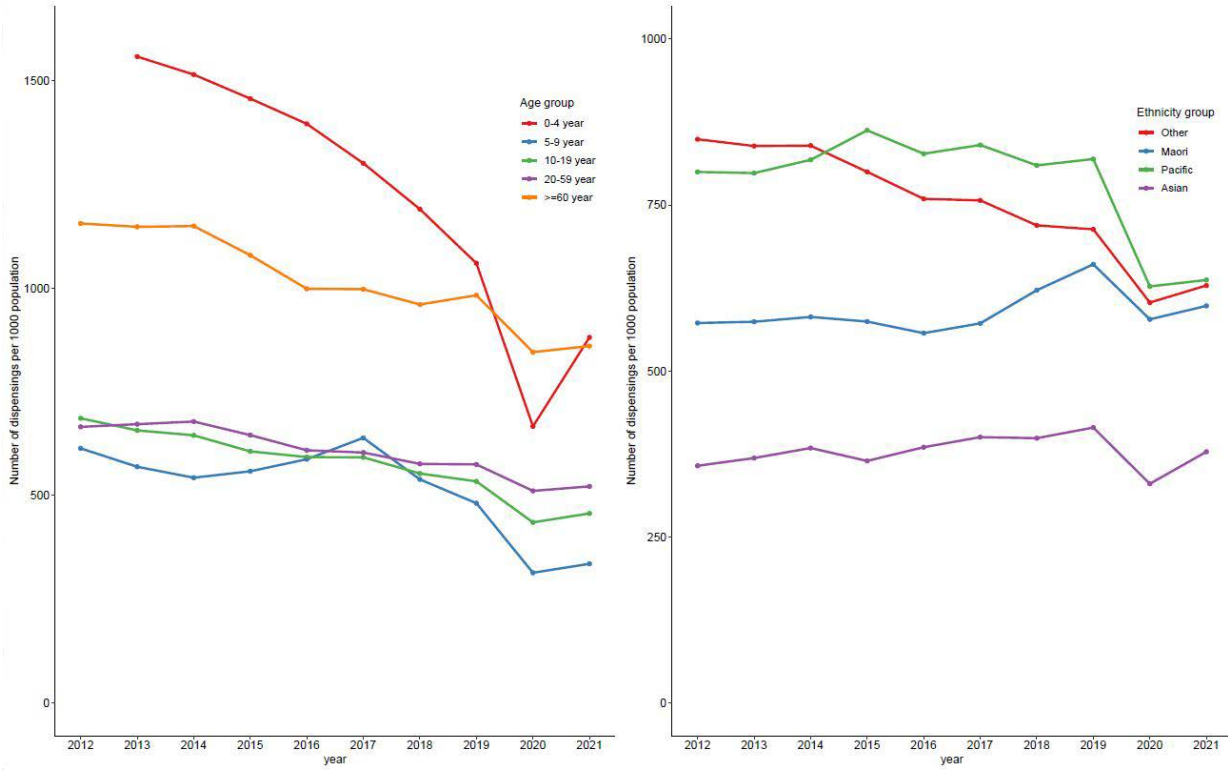


Figure 2: Antibiotic dispensing stratified per age groups (2a) and per ethnicity groups (2b).



Antibiotic dispensing per AWaRe groups

Between 2012 and 2021, the antibiotic dispensing of WHO Access and Watch antibiotics decreased (see Appendix 3). The proportion of antibiotics which were Watch antibiotics decreased as well (dispensings 22.0% to 11.9%; DIDs 17.8% to 10.4%).

Stratification per age group and ethnicity and per age group

Between 2012–2021, reductions in number of dispensings were observed in all age groups. The largest decrease was observed in those <5 years of age (AAC -7.6% [95%CI -7.7 to -7.5]) followed by those 5–9 years (AAC -5.4% [95%CI -5.5 to -5.2]), and 10–19 years (AAC -4.5% [-4.6 to -4.4]) (Figure 2a; Appendix 4). For the period 2012 to 2019, similar results were observed for number of dispensings with the largest decrease in those <5 years of age (AAC -5.6% [95%CI -5.7 to -5.5]).

In addition, number of dispensings remained similar in people with Asian ethnicity. Number of dispensings were reduced in Pacific peoples and other ethnicities, but increased in Māori (554 to 562 dispensings per 1,000 inhabitants, AAC 0.7% [95%CI 0.6 to 0.9]). (Figure 2b; Appendix 4).

Discussion

In this longitudinal study in the Waitaha Canterbury Region of Aotearoa New Zealand, community antibiotic consumption decreased significantly from 2012 through 2021. Over this decade, the number of dispensings decreased by 31%, and the DIDs by 21%. In the pre-COVID period from 2012 to 2019, the number of dispensings decreased with 21% and DIDs by 17%. The largest decline in antibiotic dispensings occurred in young children. Importantly, the proportion of WHO Watch antibiotics also decreased. However, whilst reductions were observed for the majority of antibiotic groups including quinolones, penicillins with extended spectrum, and combinations of penicillins with beta-lactamase inhibitors, dispensing of first generation cephalosporins showed a large increase.

Our study confirms that Waitaha Canterbury displays the ongoing decreasing trend for community antibiotic dispensing reported for Aotearoa New Zealand across 2015 to 2018.[9] From 2013 to 2018, antibiotic dispensing in Waitaha Canterbury was on average 3.7 DIDs lower than for the whole of Aotearoa New Zealand. Therefore, the decrease observed in Canterbury from 2012 to 2021 may not be generalisable to other regions in Aotearoa New Zealand. Compared to other high-income countries, the magnitude of the difference in average community antibiotic consumption between Waitaha Canterbury and the European union has decreased (3.5 DIDs in 2012 to 1.9 DIDs in 2020; Appendix 5). Nevertheless, community antibiotic dispensing in Waitaha Canterbury was higher than in Canada, the United Kingdom and 21 of 28 European countries in 2020.[14,20,21] The higher rate of antibiotic consumption in Aotearoa New Zealand might be partly explained by a higher burden of infectious disease in Māori and Pacific peoples, and the higher incidence of acute rheumatic fever in these groups.[22] The latter risk means that Aotearoa New Zealand prescribers are advised to consider the need for antibiotics in young people presenting with possible streptococcal infections, in particular those presenting with sore throats.

In our study, differences in antibiotic consumption across ethnicity groups reduced over time. Antibiotic consumption decreased mainly in people with other ethnicities and Pacific people whereas Māori had a minimal increase in antibiotic consumption. Considering the increased burden of infectious diseases in Māori and Pacific people,[22] Thomas et al. suggested antibiotic targets for Aotearoa New Zealand to be 2.5 dispensings per 1,000 inhabitants per day for Māori and Pacific peoples, and 1.5 for Other ethnicities.[9,23] Our study shows that antibiotic dispensings for Asian and Other ethnicities are close to these suggested targets (antibiotic dispensings per 1,000 inhabitants per day: Other 1.7; Asian 1.0), but the reduced dispensings for Māori and Pacific peoples are potentially of concern (antibiotic dispensings per 1000 inhabitants per day: Māori: 1.6; Pacific peoples 1.7).

The COVID-19 pandemic has largely influenced antibiotic dispensings. Our finding of a 16% reduction in antibiotic dispensing in the year 2020 was also reported by Duffy et al. who reported a 36% decrease for the whole of Aotearoa New Zealand comparing antibiotic consumption before and after implementation of public health interventions in response to the COVID-19 pandemic.[19] The decrease in 2020 can be partly explained by a lower incidence of infections due to social distancing. In our study, the increase in antibiotic dispensing from 2020 to 2021, which was mainly due to increased dispensings of penicillins with extended spectrum, may be explained by an increase in infections due to increased social interactions after lockdown restrictions were eased, but it may also represent

potentially avoidable antibiotic use. It should be noted that the level of restrictions in Waitaha Canterbury have been less impactful compared to other districts in Aotearoa New Zealand in 2020 and 2021.

The WHO AWaRe guideline recommends that >60% of antibiotic dispensings are Access antibiotics in the hospital and in the community.[12] In our study including only community antibiotic dispensing, the proportion of Access antibiotics increased from 82% to 87% across 2012 to 2021. Other international studies that report on the WHO AWaRe classification have focussed on total antibiotic consumption or hospital consumption, and have not reported community dispensing separately.[12,24–26] Insight into both community and hospital antibiotic consumption using a uniform definition such as the AWaRe classification is important to inform antimicrobial stewardship programs, and to compare antibiotic consumption internationally.

Aotearoa New Zealand has an antimicrobial resistance action plan (2017) but does not currently have sector-wide national antimicrobial stewardship leadership, or activities. However, positive work has commenced, for instance via national organisations and local antimicrobial stewardship groups.[27,28] In our study, a decrease in antibiotic dispensing was observed in antibiotic agents that are known to have increasing rates of antimicrobial resistance, for example quinolones and macrolides. In Aotearoa New Zealand, the use of quinolones has been discouraged by guideline changes, antimicrobial stewardship awareness campaigns, and education on rational use resulting in a reduction of almost 80%.

Dispensing of first-generation cephalosporins increased more than 10-fold, which was attributable to an increase in cefalexin. Cefalexin dispensings increased in all age groups, and was highest in children <5 years and those ≥60 years (data not shown). In Australia, cefalexin is now the most frequently prescribed antibiotic accounting for almost one-quarter of antibiotic prescriptions in general practice.[13] In Aotearoa New Zealand, changes in national guidelines, local guidelines, and prescriptions of hospital specialists could have contributed to cefalexin dispensings. First, cefalexin is increasingly recommended as an alternative option in case of mild penicillin allergy or intolerance for flucloxacillin.[29] Second, cefalexin is now included in the list of antibiotics suitable for use in urinary tract infections in place of quinolones, and since 2016 cefalexin has been recommended as a second-line option for cystitis treatment in children. Third, guidance for the treatment for minor skin infections has changed from topical antibiotics to skin hygiene advice, and oral flucloxacillin for more wide spread infections is advised.[30] The liquid formulation of cefalexin, however, is considered more palatable compared to flucloxacillin, an important consideration in children. It is not possible to deduce from our study whether the observed increase of cefalexin is of concern since data on infection focus, allergies or previous antibiotic prescriptions were not available in our data. Further research focussing on the indications and reasons for the increasing use of cefalexin in the community is warranted.

Strengths of our study include the longitudinal nature of dispensing data for the Waitaha Canterbury Region of Aotearoa New Zealand. Second, we reported different measures of antibiotic consumption, including DIDs and number of dispensings.[15] In addition, this is the first study reporting WHO AWaRe categories in the community in Aotearoa New Zealand.

Our study has some limitations. First, we focussed on all community antibiotic dispensings, which is expected to capture the vast majority of community systemic antibiotic usage in the Region. Some antibiotics are supplied via other routes such as direct supply by a general practitioner in emergencies. Another route not included is pharmacist supply of trimethoprim, which has been available to women with uncomplicated cystitis without prescription since 2012. In our study, we observed a decrease in trimethoprim and sulphonamides; 70% of this decrease was due to reduced dispensing of trimethoprim. This decrease could be partly explained by the guideline change of first-line agent from trimethoprim to nitrofurantoin for cystitis due to increasing *E. coli* resistance. Data for pharmacist-supplied trimethoprim are not available, so it is unclear to what extent this decrease in trimethoprim dispensing has been substituted by pharmacist supplied provision of this agent. These are data that should be recorded and made publicly available. Second, we applied the defined daily dose in children although this method does not consider child-specific dosages. It is unlikely that this has influenced our results as the proportion of children <15 years has been stable (~20%) during the study period. Lastly, we did not have access to individual data

on medical history or presenting symptoms, so we were unable to determine the indication or appropriateness of antibiotic dispensings.

Conclusion

Community antibiotic dispensing decreased in Waitaha Canterbury Aotearoa New Zealand during the past decade (2012–2021). This brings the Region's community antibiotic consumption more closely in line with consumption in other high-income countries. In addition, reductions were observed in WHO Watch antibiotics such as quinolones and macrolides which may help reduce development of antimicrobial resistance. Despite these encouraging changes, current use still exceeds that in other similar countries and other published Aotearoa New Zealand data indicate that we can still further reduce antibiotic consumption without compromising health outcomes. Dispensing of cefalexin, however, increased over 10-fold. Further research should investigate which factors may be driving use of this broad-spectrum agent.

COMPETING INTERESTS
Nil.

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Appendices

Appendix 1: Anatomic therapeutic chemical classification of funded systemic antibiotics

ATC group[1]	Antibiotic agent	AWaRe classification[2]
J01A: Tetracyclines	Doxycycline, Minocycline, Tetracycline	Access
J01C: Penicillins		
J01CA: Penicillins with extended spectrum	Amoxicillin	Access
J01CE: β-lactamase-sensitive penicillins	Phenoxymethylpenicillin, Benzylpenicillin, Benzathine penicillin, Procaine penicillin	Access
J01CF: β-lactamase-resistant penicillins	Flucloxacillin	Access
J01CR: Combinations of penicillins with beta-lactamase inhibitors	Amoxicillin and clavulanic acid	Access
J01D: Cephalosporins		
J01DB: First generation cephalosporins	Cefalexin, Cefazolin	Access
J01DC: Second generation cephalosporins	Cefaclor, Cefuroxime	Watch
J01DD: Third generation cephalosporins	Ceftriaxone	Watch
J01E: Sulfonamides and trimethoprim	Trimethoprim, Trimethoprim and sulfamethoxazole	Access
J01F: Macrolides and lincosamides		
J01FA: Macrolides	Azithromycin, Clarithromycin, Erythromycin, Roxithromycin	Watch
J01FF: Lincosamides	Clindamycin	Access
J01M: Quinolones	Ciprofloxacin, Moxifloxacin, Norfloxacin	Watch
J01X: Other antibacterials		
J01XA: Glycopeptides	Vancomycin	Watch
J01XE: Nitrofuran derivatives	Metronidazole, Ornidazole	Access
J01XE: Nitrofuran derivatives	Nitrofurantoin	Access
J01XX: Other	Colistin, Gentamicin, Methenamine, Sodium fusidate, Tobramycin, Vancomycin	Reserve, Access, Unclassified, Access, Watch, Watch

[1] WHO Collaborating Centre for Drug Statistics Methodology. International language for drug utilization research. Edition., [updated 14/11/2021; cited 10/03/2022.Available from: https://www.whocc.no/atc_ddd_index/

[2] Geneva: World Health Organization. WHO Access, Watch, Reserve (AWaRe) classification of antibiotics for evaluation and monitoring of use. 2021.

Appendix 2a: Antibiotic dispensings per antibiotic groups, stratified for 2012 to 2021, and 2012 to 2019.

Antibiotic groups—number of dispensings per 1000 inhabitants per year						
Antibiotic group	**Number of dispensings per 1,000 inhabitants, year 2012**	**Number of dispensings per 1,000 inhabitants, year 2021**	**Delta: 2021 minus 2012 for number dispensings per 1,000 inhabitants**	**Average annual change between 2012–2021, RR (95% CI)**	**Delta: 2019 minus 2012 for number dispensings per 1,000 inhabitants**	**Average annual change in number of dispensings per 1,000 inhabitants between 2012–2019 RR (95% CI)**
β-lactamase-sensitive penicillins	38	18	-20	-6.7 (-6.9 to -6.6)	-15	-4.3 (-4.5 to -4)
β-lactamase-resistant penicillins	108	87	-21	-2.5 (-2.6 to -2.4)	-15	-2.4 (-2.5 to -2.3)
Penicillins with extended spectrum	201	139	-62	-4.8 (-4.9 to -4.8)	-31	-2.6 (-2.7 to -2.5)
Combinations of penicillins with betalactamase inhibitors	134	91	-43	-4.5 (-4.6 to -4.4)	-37	-4.7 (-4.8 to -4.6)
Macrolides and lincosamides	124	54	-70	-8.4 (-8.5 to -8.3)	-51	-7.1 (-7.3 to -7)
First generation cephalosporins*	3	38	35	28.1 (27.7 to 28.4)	20	29.4 (28.9 to 30)
Second generation cephalosporins	19	9	-9	-6.2 (-6.4 to -5.9)	-2	-2.7 (-3 to -2.4)
Third generation cephalosporin	0	1	1	14.1 (12.8 to 15.4)	1	21.7 (19.7 to 23.8)
Tetracyclines	65	47	-18	-3.7 (-3.8 to -3.6)	-10	-3 (-3.1 to -2.8)
Quinolones	49	11	-39	-14.6 (-14.8 to -14.5)	-32	-14.5 (-14.8 to -14.3)
Sulfonamides and trimethoprim	76	42	-35	-5.7 (-5.8 to -5.6)	-18	-3.5 (-3.7 to -3.4)
Nitrofuran derivatives	19	34	14	6 (5.8 to 6.2)	3	0.9 (0.6 to 1.2)
Imidazole derivatives	28	28	0	-1.2 (-1.4 to -1.1)	0	-0.9 (-1.2 to -0.7)
Other+	0.6	3.1	2.5	21.6 (20.5 to 22.8)	0.3	3.5 (2 to 5.1)

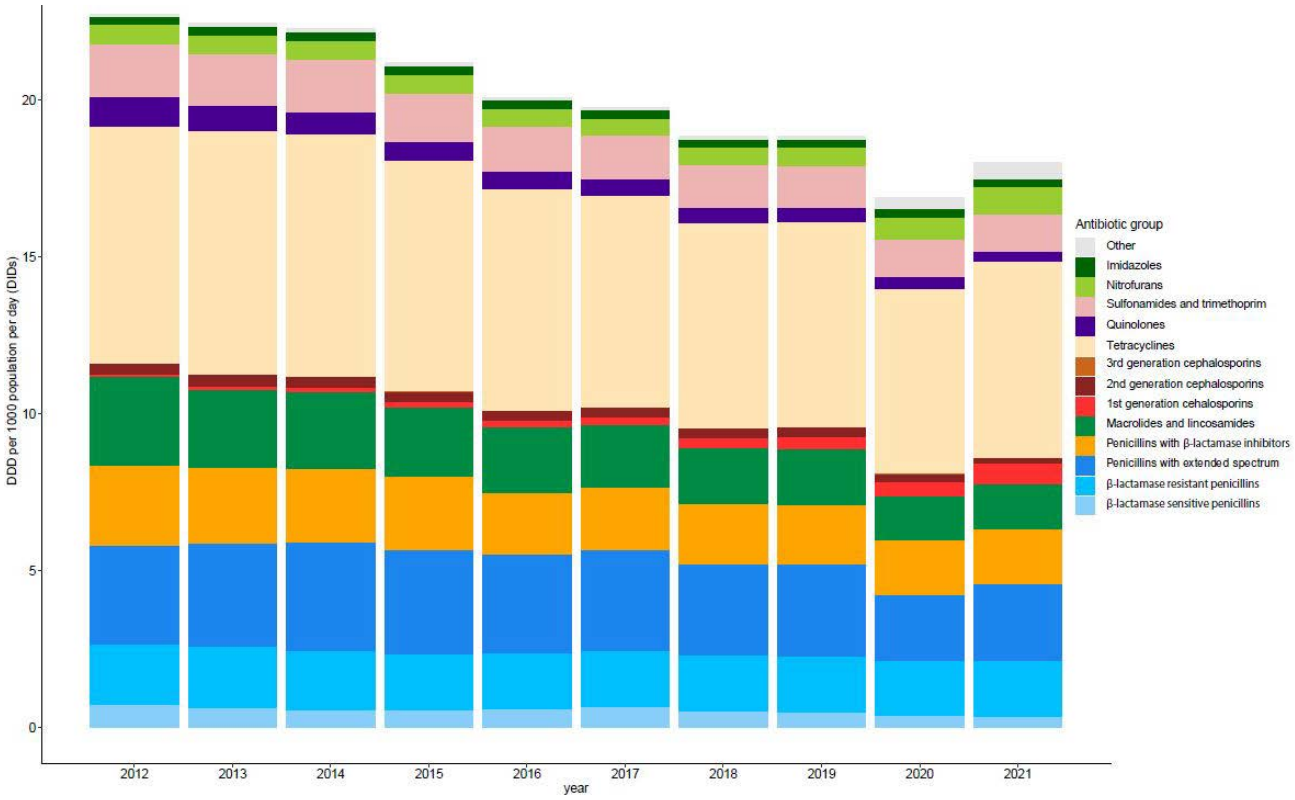
*Increase in first-generation cephalosporins mainly attributable to increases in cefalexin
+ Increase in other antibiotics mainly attributable to increases in methenamine hippurate

Appendix 2a (continued): Antibiotic dispensings per antibiotic groups, stratified for 2012 to 2021, and 2012 to 2019.

Antibiotic groups—defined daily doses per 1000 inhabitants per day (DIDs)						
Antibiotic group	**DIDs, year 2012**	**DIDs, year 2021**	**Delta 2021 minus 2012 for DIDs**	**Average annual change in DIDs between 2012–2021, Beta (95% CI)**	**Delta: 2019 minus 2012 for DIDs**	**Average annual change in DIDs between 2012–2019, Beta (95% CI)**
β-lactamase-sensitive penicillins	0.73	0.36	-0.37	-0.03 (-0.05 to -0.02)	-0.24	-0.02 (-0.04 to 0)
β-lactamase-resistant penicillins	1.92	1.76	-0.15	-0.02 (-0.03 to -0.01)	-0.14	-0.03 (-0.04 to -0.02)
Penicillins with extended spectrum	3.15	2.47	-0.69	-0.11 (-0.17 to -0.05)	-0.19	-0.05 (-0.09 to -0.01)
Combinations of penicillins with betalactamase inhibitors	2.58	1.74	-0.84	-0.1 (-0.11 to -0.08)	-0.68	-0.1 (-0.13 to -0.08)
Macrolides and lincosamides	2.83	1.43	-1.40	-0.15 (-0.17 to -0.13)	-1.07	-0.15 (-0.17 to -0.13)
First generation cephalosporins*	0.07	0.67	0.60	0.06 (0.05 - 0.07)	0.33	0.04 (0.04 to 0.05)
Second generation cephalosporins	0.33	0.17	-0.16	-0.02 (-0.02 to -0.01)	-0.02	-0.01 (-0.01 to 0)
Third generation cephalosporin	0.00	0.01	0.00	0 (0 to 0)	0.00	0 (0 to 0)
Tetracyclines	7.58	6.27	-1.31	-0.2 (-0.25 to -0.16)	-1.05	-0.2 (-0.25 to -0.14)
Quinolones	0.93	0.32	-0.61	-0.06 (-0.07 to -0.05)	-0.49	-0.07 (-0.08 to -0.05)
Sulfonamides and trimethoprim	1.69	1.19	-0.50	-0.06 (-0.07 to -0.05)	-0.34	-0.05 (-0.07 to -0.04)
Nitrofuran derivatives	0.61	0.85	0.24	0.01 (0 to 0.03)	-0.04	-0.01 (-0.02 to 0)
Imidazole derivatives	0.24	0.26	0.02	0 (0 to 0)	0.01	0 (-0.01 to 0)
Other+	0.09	0.53	0.44	0.04 (0.01 to 0.06)	0.04	0 (0 to 0.01)

* Increase in first-generation cephalosporins mainly attributable to increases in cefalexin.
\+ Increase in other antibiotics mainly attributable to increases in methenamine hippurate.

Appendix 2b: Defined daily doses per 1,000 inhabitants per day (DIDs) per antibiotic group



Appendix 3a: Analysis per WHO AWaRe groups

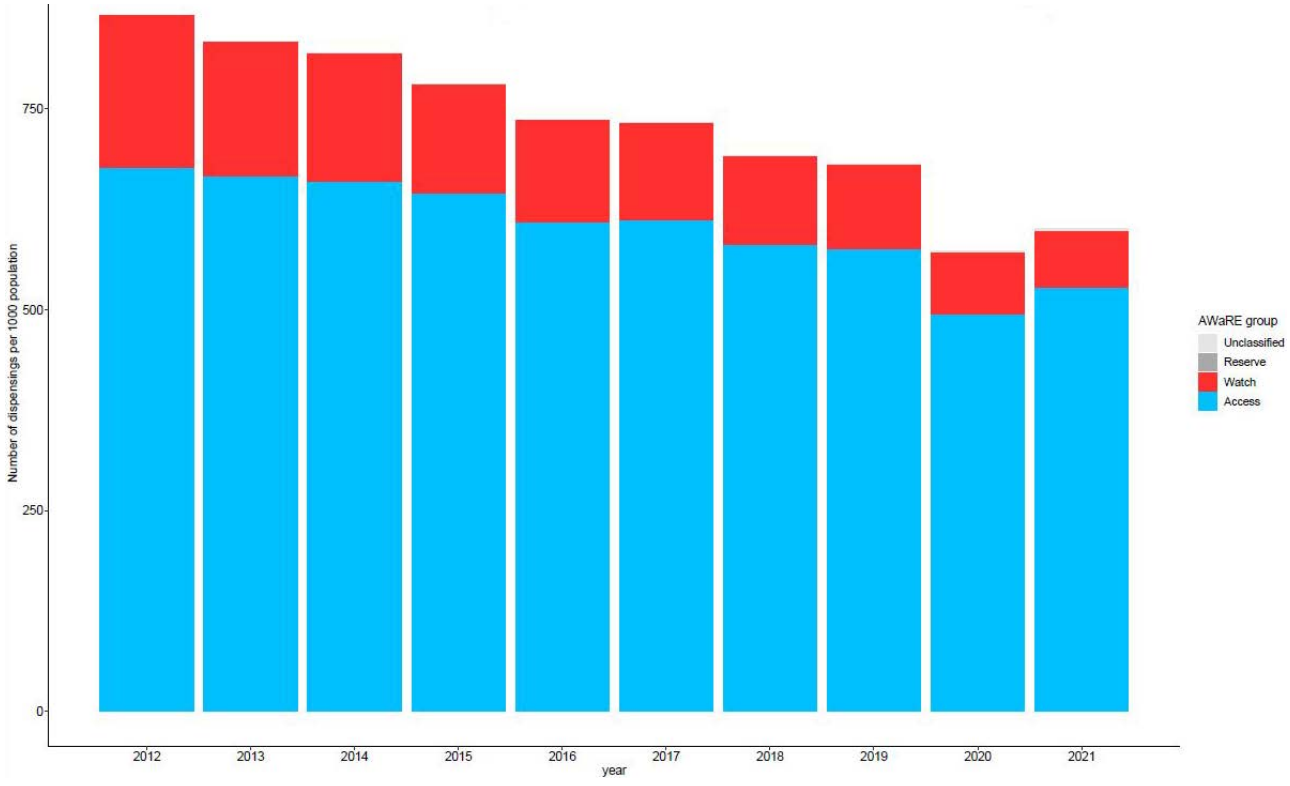
WHO AWaRe groups —number of dispensings per 1,000 inhabitants per year						
AWaRe	**Number of dispensings per 1,000 inhabitants, year 2012**	**Number of dispensings per 1,000 inhabitants, year 2021**	**Delta 2021 to 2012 for number dispensings per 1,000 inhabitants**	**Average annual change between 2012-2021, RR (95% CI)**	**Delta: 2019 minus 2012 for number dispensings per 1,000 inhabitants**	**Average annual change in number of dispensings 2012–2019 RR (95% CI)**
Access	675	527	-149	-3.2 (-3.2 to -3.1)	-101	-3.2 (-3.3 to -3.2)
Watch	191	71	-120	9.5 (-9.6 to -9.5)	-85	-9.9 (-10 to -9.8)
Reserve	0	0	0	12.1 (1.8 to 23.9)	0	14.5 (2.2 to 29.1)
Unclassified	0	3	2	26.7 (25.3 to 28.1)	0	17.6 (16.1 to 19.2)

Appendix 3a (continued): Analysis per WHO AWaRe groups

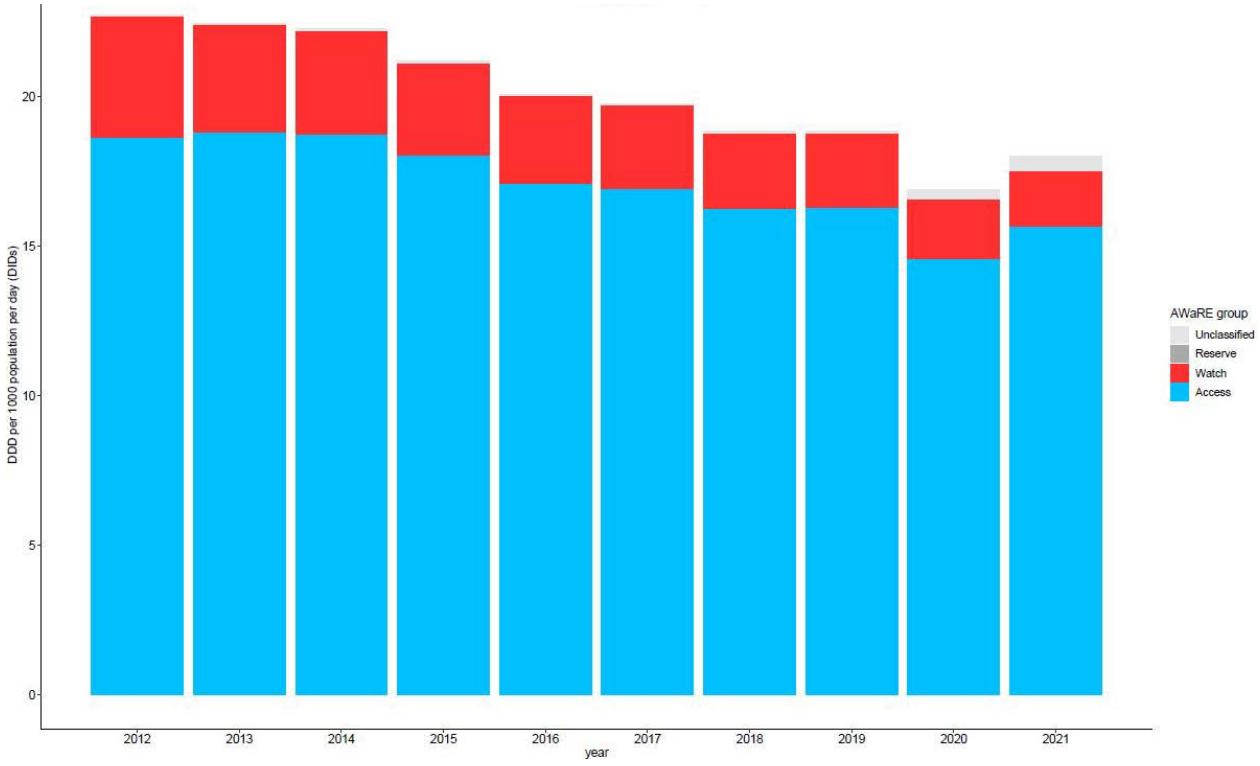
WHO AWaRe groups—defined daily doses per 1,000 inhabitants per day (DIDs) per antibiotic group						
AWaRe	**DIDs, year 2012**	**DIDs, year 2021**	**Delta 2021 to 2012 for DIDs**	**Average annual change in DIDs between 2012–2021, Beta (95% CI)**	**Delta: 2019 minus 2012 for DIDs**	**Average annual change in DIDs Beta (95% CI)**
Access	18.6	15.6	-3.0	-0.45 (-0.56 to -0.34)	-2.35	-0.42 (-0.53 to -0.32)
Watch	4.1	1.9	-2.2	-0.23 (-0.25 to -0.21)	-1.57	-0.22 (-0.26 to -0.19)
Reserve	0.0	0.0	0.0	0 (0 to 0)	0.00	0 (0 to 0)
Unclassified	0.1	0.5	0.4	0.04 (0.01 to 0.06)	0.04	0 (0 to 0.01)

DIDs: Defined daily doses per 1,000 inhabitants per day.

Appendix 3b: Dispensings per 1,000 inhabitants per WHO AWaRE group (figure).



Appendix 3c: Defined daily doses per 1,000 inhabitants per day (DIDs) per WHO AWaRe group (figure).



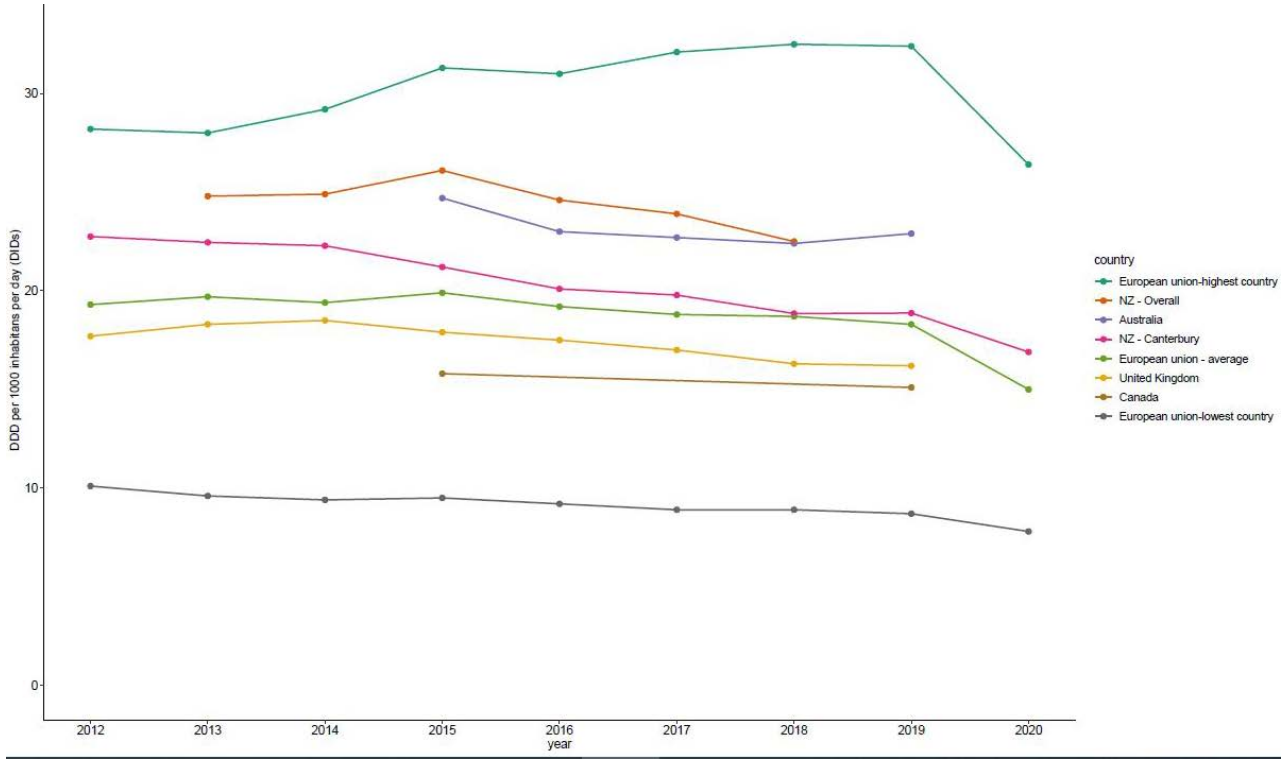
Appendix 4a: Stratified analysis for age and ethnicity.

Age groups—number of dispensings per 1,000 inhabitants per year						
Age groups	**Number of dispensings per 1,000 inhabitants year 2012**	**Number of dispensings per 1,000 inhabitants year 2021**	**Delta 2021 to 2012 for number dispensings per 1,000 inhabitants**	**Average annual change between 2012–2021, RR (95% CI)**	**Delta 2019 to 2012 for number dispensings per 1,000 inhabitants**	**Average annual change between 2012-2019, RR (95% CI)**
0–4 years	1,652	881	-772	-7.6 (-7.7 to -7.5)	-593	-5.6 (-5.7 to -5.5)
5–9 years	613	335	-278	-5.4 (-5.5 to -5.2)	-132	-1.6 (-1.8 to -1.4)
10–19 years	686	456	-229	-4.5 (-4.6 to -4.4)	-152	-3.4 (-3.5 to -3.2)
20–19 years	665	521	-144	-3.1 (-3.2 to -3.1)	-91	-2.6 (-2.7 to -2.5)
60 years and above	1,155	860	-296	-3.5 (-3.6 to -3.5)	-173	-3 (-3 to -2.9)

Appendix 4a (continued): Stratified analysis for age and ethnicity.

Ethnicity groups—number of dispensings per 1,000 inhabitants per year						
Ethnicity groups	**Number of dispensings per 1,000 year 2012**	**Number of dispensings per 1,000 year 2021**	**Delta 2021 to 2012 for number dispensings per 1,000**	**Average annual change between 2012–2021, RR (95% CI)**	**Delta 2019 to 2012 for number dispensings per 1,000 inhabitants**	**Average annual change between 2012–2019, RR (95% CI)**
Other	849	629	-220	-3.6 (-3.6 to -3.6)	-136	-2.8 (-2.8 to -2.7)
Māori	572	598	26	0.8 (0.7 to 1)	88	1.7 (1.5 to 1.9)
Pacific peoples	800	637	-163	-2.3 (-2.5 to -2.1)	19	0.3 (0 to 0.6)
Asian	357	378	-21	0.1 (0 to 0.3)	58	2 (1.8 to 2.2)

Appendix 5: International comparison for defined daily doses per 1,000 inhabitants per day.



Percutaneous vertebroplasty: efficacy in the management of pain related to acute vertebral compression fractures

Ashreya Duvuru, Stewart Paul Hawkins

ABSTRACT

AIM: Historically, both acute and chronic vertebral compression fractures (VCF) have been managed with vertebral augmentation procedures such as percutaneous vertebroplasty (VP). Recently, however, the trend has shifted to manage VCF pharmacotherapeutically. This study aims to determine if VP is effective for managing pain related to acute VCF (≤12 weeks).

METHOD: This study retrospectively surveyed 8 of 15 patients that underwent VP at Middlemore Hospital between 2018 and 2021. All had VCF aged ≤12 weeks, and presence of increased bone marrow signal on magnetic resonance imaging (MRI). The survey reviewed pain levels (via numeric score), opiate analgesia dispensation, and mobility levels pre- and post-procedure.

RESULTS: Results showed post-procedure improvement in pain levels in 75% of individuals, which were maintained over the two- and four-week marks. There was an improvement in mobility in 75% of patients at 4 weeks, and 66% had decreased dispensation or complete cessation of opioid analgesia 4 weeks post procedure.

CONCLUSION: This study shows that VP correlates with overall improvement in pain scores, opiate use and mobility in the sample group with VCF aged ≤12 weeks. Hopefully the results of this study will encourage physicians to consider vertebroplasty as a method of achieving adequate analgesia in this demographic of patients.

As New Zealand's ageing population grows, the prevalence of osteoporosis and related complications grow with it. Vertebral body compression fractures (VCF) are the most common osteoporotic fracture, occurring in 20% of people over the age of 70 years.[1] VCFs generally present with significant pain and loss of mobility. They are diagnosed by correlating clinical history and examination with imaging. Radiographic findings on X-ray, computed tomography (CT) and magnetic resonance imaging (MRI) include loss of vertebral body height, high density suggestive of bone compression, and sometimes overt fractures. A decrease in vertebral height of 20% or more, or a decrease of at least 4mm compared with baseline height is considered positive for compression fracture.[2]

To determine if a fracture is acute or chronic, clinical history is correlated with imaging. Evidence of acute fracture includes cortical breaking or impaction of trabeculae. The absence of these signs indicates a chronic fracture. MRI characteristically demonstrates oedema in acute fractures with a high bone marrow signal on short-TI inversion recovery (STIR) weighted scans, and MRI can help determine the age of a fracture. Isotope bone scans can also differentiate between acute and chronic compression fractures, as acute fractures will appear "hot" with increased radio-isotope up-take.[3,4]

As pain is the hallmark feature of VCF, analgesia is paramount in management.[5] Elderly patients, who are more predisposed to developing acute VCFs, are at greater risk of developing adverse effects of analgesia such as constipation, falls and nausea.[6] They are also at high risk of becoming deconditioned due to a prolonged period of limited mobility and are prone to developing secondary conditions such as bed sores and pneumonia.

Standard practice has been to manage a VCF with oral analgesia, and perform percutaneous vertebroplasty or kyphoplasty ("vertebral augmentation", or VA) if there has been no improvement in pain. Percutaneous vertebroplasty is a minimally invasive procedure in which radio-opaque cement (polymethyl methacrylate- PMMA) is injected into the affected vertebral bodies under fluoroscopic guidance.[3] This in turn leads to stabilisation of the fracture and provides effective pain relief.

This retrospective single-centre study was undertaken to investigate the efficacy of vertebroplasty as performed at Middlemore Hospital. This is specifically in patients who had one or more acute vertebral compression fractures, all aged

12 weeks or less and positive for acute fracture-oedema on MRI. By doing this, the study was able to isolate the group thought to better respond to vertebroplasty as a means of analgesia. We hypothesised that there would be an improvement in pain scores in those that had received the procedure.

Aim

To determine if percutaneous vertebroplasty is effective in managing pain in patients with acute vertebral body compression fractures.

Method

Design: retrospective study

Setting

Fifteen consecutive patients underwent percutaneous vertebroplasty for the treatment of one or more acute vertebral insufficiency fractures at Middlemore Hospital, Counties Manukau District Health Board (CMDHB), Auckland between 2018 and 2021. All 15 patients in the cohort had a fracture age of 12 weeks or less, with the presence of increased bone marrow signal on MRI.

Prior to collating data for the study, approval was gained from the Auckland Health Research Ethics Committee (reference number: AH23296).

Participants were contacted over the phone and consented to participate in the study. They were surveyed with a questionnaire, which covered pain scores (based on the numeric pain rating scale), amount of analgesia used, and mobility pre- and post-procedure.

A secondary wing of the study analysed doses of opioid analgesia consumed prior to and following the procedure, according to outpatient medicine dispensing records. Community dispensing records were obtained to analyse the doses of opioids dispensed to look for trends in use of analgesia pre- and post-procedure.

Participants

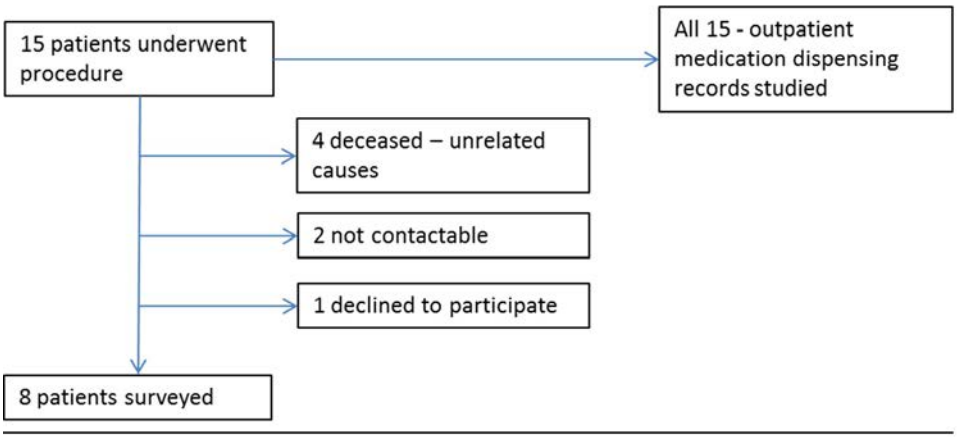
Of the fifteen patients in the initial group, four patients were deceased, two were not contactable, and one declined to participate in the survey, resulting in eight out of fifteen that participated in the survey element.

Results

The illustrative vignette below demonstrates clinical history and imaging used in the process of selection, post procedure imaging and clinical outcome.

An elderly female presented with acute lumbar spine pain following a fall. She experienced severe pain requiring opiates and could not mobilise during a week-long admission. MRI confirmed the suspicious fracture of L3 but also the plain film and CT *occult* fracture of L4.

Figure 1: Study method.



[Flowchart 1 – Study Method]

Figures 2–6

After two-level vertebroplasty the patient had immediate pain relief was able to mobilise and was discharged the following day on simple analgesia.

Of the eight patients in our study that participated in the survey, six patients described improvement in pain scores immediately after the procedure. Of the six, all reported either improvement or consistently similar improved pain levels 2 weeks and 1 month following the procedure. One patient reported improvement after 2 weeks, while one reported no improvement at all in pain levels following the procedure.

The average pain score among the participants preceding the procedure was 9.25/10. The average pain score immediately following the procedure was 4.375/10. The average pain scores at 2 weeks and 1 month were 3.75/10 and 2.25/10 respectively.

Of the eight participants surveyed, six felt they had improved mobility following the percutaneous vertebroplasty procedure, and two felt no improvement in mobility.

Of the four deceased (all causes not pertaining to the procedure itself), clinical notes/letters identified improvement in pain levels in all four, though not quantified as a pain score.

There were no procedure-related complications in any patient.

Of the fifteen patients, ten showed decreased amounts or complete cessation of opioid analgesia dispensed within the course of 4 weeks. Four patients had an increased dose of opiates following the initial fracture, which stayed the same post procedure. Interestingly, the one patient that reported no improvement in pain scores post procedure had decreased prescription of opiate analgesia in the community.

Figure 2: Sagittal lumbar spine plain film.
Minor superior end plate herniation of L2. Loss of height and increased density of inferior aspect of L3, suggesting fracture.

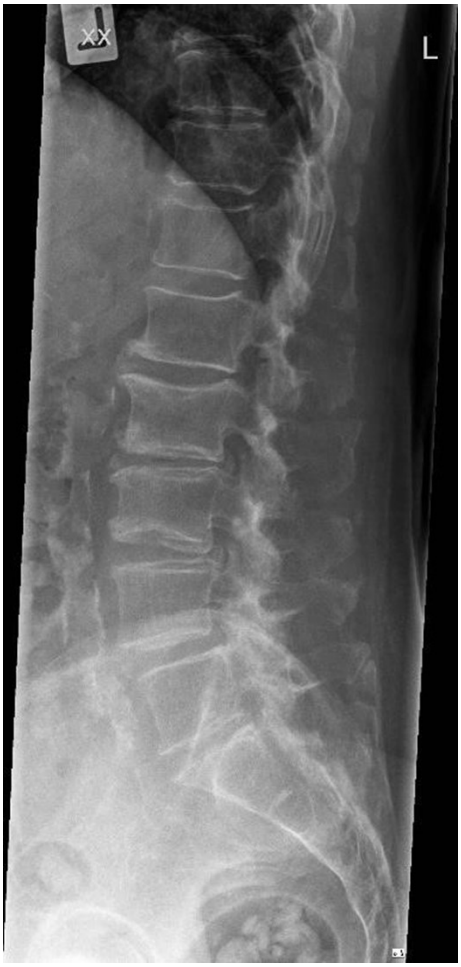


Figure 3: Sagittal reconstruction CT.
L2 changes likely old, L3 changes suggest fracture.

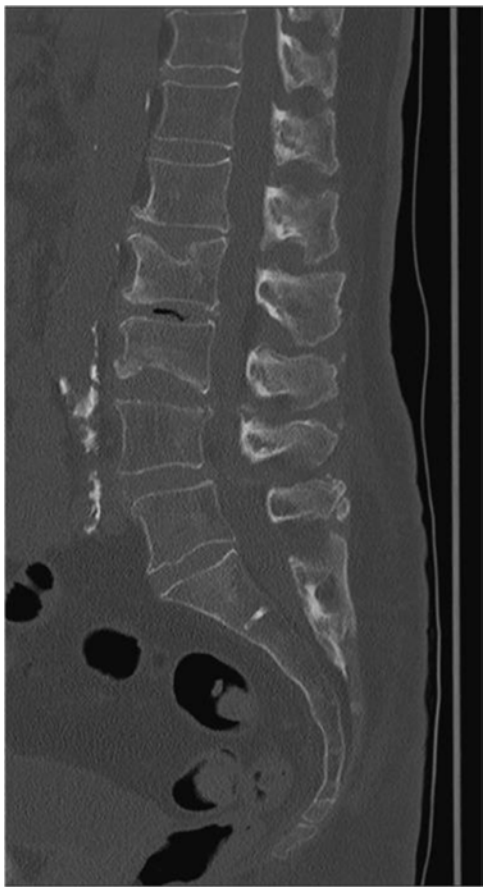
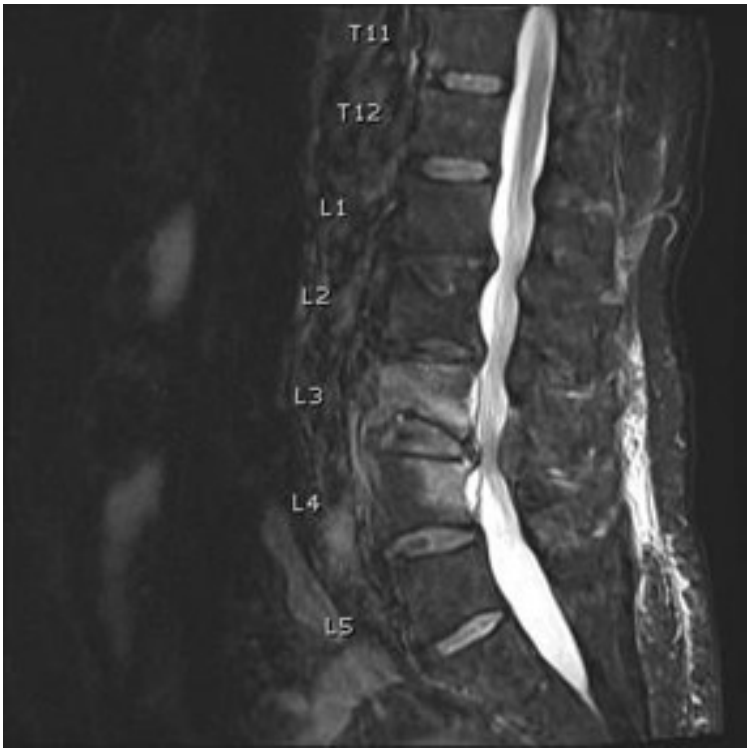
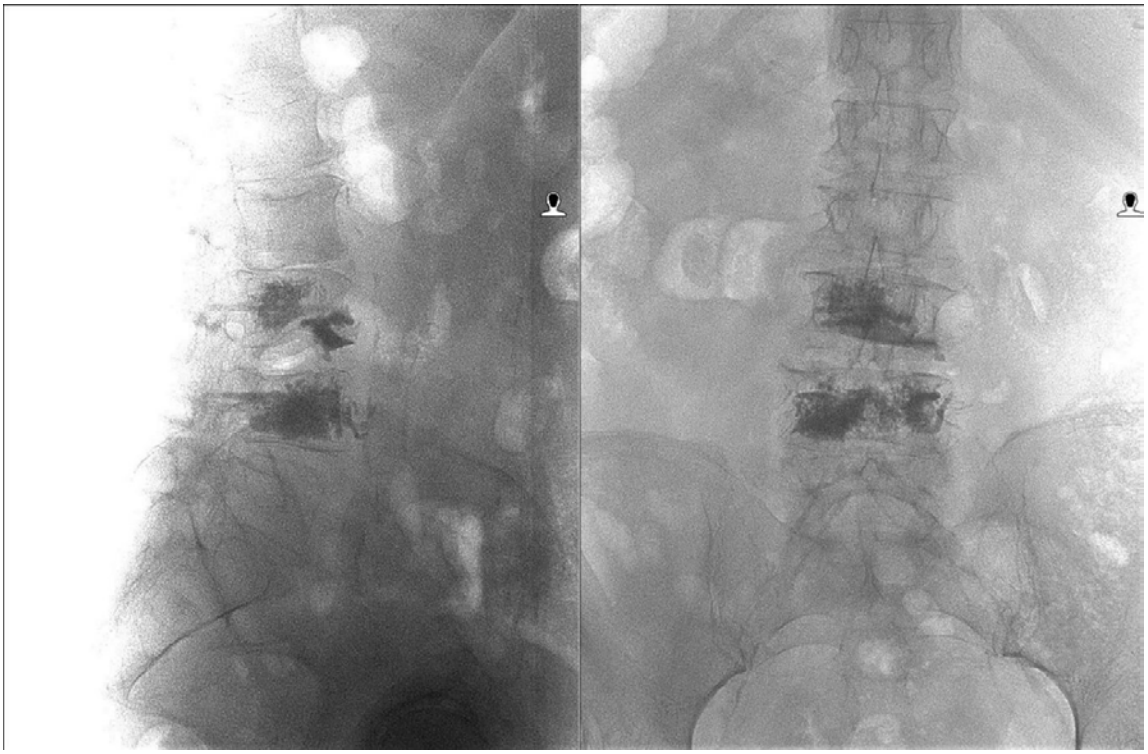


Figure 4: Sagittal STIR-weighted MRI. No oedema in L2 confirms no acute fracture. Acute fracture oedema shown in both L3 and L4.



Figures 5 & 6: Frontal and sagittal views from a rotational cone-beam CT post vertebroplasty of L3 and L4. Radio-opaque cement is seen to fill the vertebra across the midline at both levels.



Discussion

Percutaneous vertebroplasty is a modality of treatment that was first reported to be successful over forty years ago.[3] When the procedure was initially introduced at Middlemore Hospital, CMDHB, Auckland (the same hospital where this study was conducted), there was generally very good utilisation. An early study there in 2004 describes five patients with MRI evidence of acute VCF treated over a 10-month period. This small series showed good response, with near immediate improvement in pain scores for most, and delayed improvement (over the course of 6 months) in some.[7] One of the authors (SPH) noted the rapid uptake of the procedure over the years up to 2009, averaging around 10 cases per year for this 800-bed tertiary care public hospital.

Utilisation of vertebroplasty—a brief overview of the timeline

In the period 2004 to 2009 there was a 188% increase in VA procedures in the USA.[8] As the procedure became more studied, there was more controversy surrounding the efficacy of vertebroplasty.

Randomised control trials (RCTs) comparing vertebroplasty with sham procedures/placebo reported that the procedure was not effective, and not more efficacious than placebo.[9,10] The most widely discussed article was published in *The New England Journal of Medicine* (*NEJM*) in 2009 by Buchbinder et al.[10] In 2015, procedure utilisation was studied in the Medicare population in the United States. The studied population reported a 15.6% decline in volume of VA. VA includes VP and the similar procedure of percutaneous kyphoplasty, which involves an attempt to restore spinal alignment by using devices, such as balloons, to raise vertebral body height, then using cement. From a peak in 2008, after the *NEJM* publication there was a persistent decline in VA procedures up to 2018 with vertebroplasty episodes in the Medicare population falling up to 66% and VA inflation-adjusted expenditure falling 40%.[11,12]

There have been concerns about selection criteria allowing chronic fractures into these RCTs. Since 2009, other RCTs have been carried out to study the efficacy of vertebroplasty in acute VCF, and reported treatment as superior to placebo.[13–15] A multicentre randomised double-blind placebo controlled trial (VAPOUR) was conducted by Clarke et al. in 2015. The study hypothesised that early intervention by vertebroplasty is key to the management of the VCF. The VAPOUR trial had a very strict inclusion criteria of less than 6 weeks fracture age with an average fracture age of 2.8 weeks. The trial demonstrated statistically more effective analgesia in the treatment group. There was also a decrease in the length of hospital stay by 6 days and a significant decrease in the Roland Morris Disability score.[13]

A 2018 Cochrane meta-analysis of all vertebroplasty RCTs concluded that vertebroplasty is not more efficacious in the management of the VCF.[16]

Dr William Clark, the primary investigator in the VAPOUR trial, eloquently described the drawbacks of the Cochrane metanalysis in an article published in *The British Medical Journal* (*BMJ*).[17] Trials that showed overall better outcomes in the test groups had a strict inclusion criteria of *acute* compression fractures. Referenced in this response, were the VAPOUR trial (mean fracture age 2.8 weeks); the Yang et al. trial (mean fracture age 1.1 weeks),[18] both of which showed better outcomes in the treatment group. The other trials referenced, in contrast, include VERTOS IV (mean fracture duration 6.1 weeks),[19] Buchbinder et al. (12 weeks),[10] Kallmes et al. (23 weeks),[9] which all had an older mean fracture age, and showed no significant improvement in analgesia between test and sham groups. Fracture age plays a critical role in the effectiveness of the vertebroplasty procedure.

Comparison of this study with others

The study, like the VAPOUR trial recruited only inpatients, with unmanageable pain requiring hospitalisation. This is unlike the VERTOS IV and Kallmes et al. trials which only recruited outpatients. Due to the comparatively strict inclusion criteria, this study only observed analgesic effect in the setting of an acute VCF. This is unlike some of the aforementioned studies which allowed for older, more chronic fractures to be included.

Strengths and limitations of this study

This study, like the VAPOUR trial, attempts to study the efficacy of vertebroplasty in the acute setting, i.e., fracture age of 12 weeks or less. However, the study design has limitations. These are the sample size and bias associated with retrospective analysis, together with recall bias. Some of the patients have also had further injuries and health issues after their procedures which resulted in requirement of analgesia. However, there was a consistent recollection of a pain-free period post procedure in those that reported improvement. There were good participation

rates particularly given the length of time since the index procedure. Of the nine patients that were contacted, eight agreed to be surveyed.

Main findings of this study

Of those patients surveyed in our study, 75% showed immediate and sustained improvement in pain and mobility of which further improved over time. The average pain score of those surveyed halved from 9.25 to 4.375 immediately after the procedure. Similar reports of immediate improvement have anecdotally been described by others.[7] The results of this study indicate that VP is a relatively reliable, safe and acceptable means of providing analgesia in acute VCFs that would not as easily be managed with pharmacologic therapy, mainly using opioids.

Implications for practice

VCFs are associated with mortality risk. From the first VCF, 3-year mortality has been found to be 46.1%, significantly higher and around double that of matched control groups, with similar and consistent findings at 5 years and 7 years post VCF, regardless of age or sex.[20]

A review of the 100% USA Medicare data set 2005–2009 found that the non-VA group had a 55% higher adjusted risk of mortality than the balloon kyphoplasty and 25% higher than the vertebroplasty treated groups. This non-operated group had higher risks of pneumonia, myocardial infarction, deep vein thrombosis and urinary tract infection.[21]

Changes in treatment patterns and outcomes of VCF before and following the 2009 sham trials have also been studied using US Medicare data. Overall, the propensity adjusted mortality of VCF increased by 4% after 2009. The 10-year mortality risk following VCF was 19% lower in the balloon kyphoplasty group, and 7% lower in the vertebroplasty group compared with the non-operative group.[22] Furthermore, in a highly clinically useful approach it has been estimated from this data that the VCF number needed to treat to "save a life" may be as low as 11.9.[23] There are theoretical benefits of balloon kyphoplasty versus vertebroplasty but these have not been adequately studied. Patient selection and suitability criteria as well as operator bias are likely to favour younger, fitter patients being offered balloon kyphoplasty.

With an ageing population, VCFs will rise in number. A 2007 analysis of the economic burden of osteoporosis in New Zealand documented 27,994 VCFs, with $NZD 212 million spent on treating fractures, and $NZD 85 million for care after fractures. A significant proportion of those costs were attributed to hospitalisation.[24] Costing obtained from Middlemore Hospital showed that a single night in a rehabilitation ward costs just over $2,600 per night (with most patients requiring over a week as inpatients to manage their pain). An MRI of the thoracolumbar spine costs $1,854 and the vertebroplasty procedure costs $2,596. The data from this study points to an immediate improvement in pain levels and mobility for these patients through percutaneous vertebroplasty, targeted to the acute period post fracture where MRI confirms the acute bone marrow oedema and thereby accurately identifies the vertebral level(s) to target. The VAPOUR trial points toward an overall reduction in hospital stay and a decrease in the economic and resource burden of each fracture event.[9]

Future directions

This paper will hopefully draw the attention of physicians caring for patients with VCFs to the weaknesses in the earlier sham trials that have reduced the utilisation of VA worldwide, and to reaffirm that VCF is not simply a benign condition requiring analgesia. VCF is strongly associated with mortality and carries a high economic burden. Suitable patients with fracture oedema demonstrated on MRI, treated within 12 weeks, and preferably earlier, by percutaneous VA are likely to respond rapidly, reliably and with a high safety margin, reducing morbidity, mortality and healthcare costs. Clinical care pathways should incorporate appropriate investigation and consideration of these patients for VA treatment.

COMPETING INTERESTS
Nil.

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Cardiac complications of COVID-19 infection

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ABSTRACT

Since the start of the COVID-19 pandemic, studies emerged reporting the occurrence of cardiovascular complications in patients affected by SARS-CoV-2. Initial data were likely skewed by higher risk populations and those with severe disease. Recent, larger studies have corroborated this association and provide estimates for risk of cardiovascular complications. Patients affected by COVID-19 are at increased risk of myocardial infarction, myocarditis, venous thromboembolism, arrhythmias, and exacerbation of heart failure. Furthermore, a subset of patients who recover from the acute illness have persistent symptoms, a condition termed "long COVID", and management of these symptoms is challenging. Clinicians treating patients affected by COVID-19 should remain vigilant for cardiac complications during the acute illness, particularly in high-risk populations.

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in late 2019 and heralded the coronavirus disease 2019 (COVID-19) pandemic. As of November 2022, there have been over 638 million reported cases of COVID-19 infection and 6.6 million fatalities worldwide.[1] New Zealand's initial years of the pandemic were characterised by a low prevalence of COVID-19 compared to other developed nations, but the country has since witnessed discrete periods of widespread community transmission, the most recent of which was the February 2022 Omicron variant outbreak. As of November 2022, there have been almost two million recorded cases of COVID-19 infection in New Zealand, representing approximately 40% of the total population, of which there were 2,212 deaths.[2]

Ever since the first global outbreak in the early months of 2020, emerging data suggested that affected patients were at increased risk of cardiovascular morbidity and mortality, particularly those with underlying risk factors or established cardiovascular disease. Furthermore, observational studies reported on the development of *de novo* cardiac pathology in otherwise healthy individuals. The long-term complications of COVID-19 infection are unknown, but evidence suggests that some patients have persistent symptoms after recovery from the index infection, which has been termed "long COVID".

As New Zealand healthcare professionals continue to face surges in infection rates of COVID-19 in the community, we present a review of the current research into the cardiac complications of COVID-19 infection (see Table 1) and recommendations as to their management.

Mechanisms of cardiac injury

Multiple potential mechanisms have been proposed to explain the acute cardiac complications of COVID-19. These include direct invasion into myocardial tissue via transmission through angiotensin converting enzyme II receptors with activation of the inflammatory pathways and cytokine activation, destabilisation of existing coronary plaques by means of inflammatory cell activation, increasing the mismatch between myocardial oxygen demand and supply due to infection, endothelial and microvascular injury, platelet activation and thrombus formation.[3–5]

Severe COVID-19 infection and mortality in patients with established cardiovascular disease

Early in the pandemic, observational studies reported an increased risk of severe COVID-19 infection and mortality in patients with established cardiovascular disease or those with risk factors. These early data were summarised by Bae et al. in their systematic review and meta-analysis of 51 studies up to June 2020,[6] which included 48,317 adult patients with confirmed COVID-19 infection. Hypertension was present in 26%, and these patients were at significantly higher risk of severe COVID-19 infection (odds ratio [OR] 2.42) and death (OR 2.60). Similarly, diabetes was present in 15% and these patients had higher risk of severe COVID-19 (OR 2.47) and death (OR 2.11). Overall, cardiovascular disease, although not defined, was present in 8%, and of note, pooled analysis showed a significantly higher risk of severe COVID-19 infection (OR 3.15) and death (OR 3.23). Findings

Table 1: Summary of study findings—COVID-19 related cardiac complications.

Cardiovascular complications	Countries	COVID-19 positive cases	Type of study	Main findings
Myocardial infarction				
Katsoularis et al. (2021)	Sweden	86,742	Nationwide database	- 2.5x increased risk of MI in the 2 weeks after COVID-19 infection.
Modin et al. (2020)	Denmark	5,119	Nationwide database	- 5.9x increased risk of MI in the 2 weeks after COVID-19 infection.
Zuin et al. (2023)	USA	1,245,157	Systematic review and meta-analysis	- MI occurs in 0.5% of COVID-19 recovered patients. - 93% higher risk acute MI in COVID-19 recovered patients (8.5 months follow-up).
Rodriguez-Leor et al. (2021)	Spain	91	Nationwide database	- 9% of STEMI patients had COVID-19. - Higher risk of HF, cardiogenic shock, stent thrombosis, and mortality in COVID-19 patients.
Garcia et al. (2021)	USA	230	Multicentre registry	- Higher rate of cardiogenic shock and less PCI in COVID-19 STEMI patients. - COVID-19 patients more likely to have no culprit lesion and be medically managed.
Gharibzadeh et al. (2021)	Brazil, USA, UK, Spain, Italy	447	Systematic review and meta-analysis	- 25% mortality in COVID-19 STEMI patients. - Cardiogenic shock in 18%, cardiac arrest in 3–28% - COVID-19 infection independent risk factor for mortality in STEMI patients.
Myocardial injury and myocarditis				
Biasco et al. (2021)	Switzerland	452	Multicentre prospective cohort	- Myocardial injury in 48% of COVID-19 patients (c.f. 65% influenza patients). - COVID-19 patients have 3.5x higher 28-day mortality compared to influenza patients.
Puntmann et al. (2020)	Germany	100	Prospective cohort	- Cardiac MRI evidence of cardiac involvement in 78% - Persistent myocardial inflammation in 60% of COVID-19 recovered patients.
CAPACITY-COVID-19 and LEOSS Study Group (2022)	18 countries	16,511	Multinational observational	- Myocarditis in 0.2% of COVID-19 patients.
Daniels et al. (2021)	USA	1,597	Multicentre observational	- Myocarditis in 2.3% (most subclinical). - Cardiac MRI increased detection of myocarditis by 7.4x.

Table 1 (continued): Summary of study findings—COVID-19 related cardiac complications.

Cardiovascular complications	Countries	COVID-19 positive cases	Type of study	Main findings
Arrhythmia				
Coromilas et al. (2021)	12 countries	4,526	International multicentre observational	- Tachyarrhythmia in 18% of COVID-19 patients (80% atrial, 20% ventricular). - Bradyarrhythmia in 22%. - High mortality in patients with arrhythmia (49% any arrhythmia; 62% for ventricular arrythmia).
Venous thromboembolism				
Knight et al. (2022)	England and Wales	1,367,059	Nationwide cohort	- Increased risk of DVT (12x) and PE (39x) in the first week after diagnosis with COVID-19. - Risk decreases over time.
Nasrullah et al. (2022)	USA	1,659,040	Nationwide database	- Hospitalised patients with COVID-19 and PE had higher need for mechanical ventilation and higher in-hospital mortality.
Heart failure				
CAPACITY-COVID-19 and LEOSS Study Group (2022)	18 countries	16,511	Multinational observational	- *de novo* HF in 0.6%. - HF associated with in-hospital mortality (RR 1.6).
Rey et al. (2020)	Spain	3,080	Single-centre prospective	- Acute HF in 2.5%, most *de novo*. - Pre-existing HF strongest risk factor for developing HF with COVID-19. - COVID-19 patients with HF had >2x mortality rate (26%) compared to those without HF.
Petrili et al. (2020)	USA	5,279	Single-centre prospective	- HF strongly associated with hospital admission (OR 4.4) and critical illness (OR 1.9).

Table 1 (continued): Summary of study findings—COVID-19 related cardiac complications.

Cardiovascular complications	Countries	COVID-19 positive cases	Type of study	Main findings
Long COVID				
Subramanian et al. (2022)	UK	486,149	National database	- Female gender, ethnic minority and socioeconomic deprivation associated with risk of long COVID. - COPD (HR 1.55), smoking (HR 1.12) and obesity (HR 1.1) were also risk factors. - Most common cardiorespiratory symptoms were shortness of breath at rest and chest pain.
Roca-Fernandez et al. (2022)	UK	534 with long COVID-19	Multicentre prospective	- 19% had abnormal baseline cardiac MRI, most with normal cardiac biomarkers. - Cardiac symptoms not predictive of cardiac impairment on MRI. - Persistent cardiac impairment in 58% of those with follow up data at 12 months.

Abbreviations: COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; HF = heart failure; MI = myocardial infarction; MRI = magnetic resonance imaging; OR = odds ratio; PCI = percutaneous coronary intervention; PE = pulmonary embolus; STEMI = ST-elevation myocardial infarction.

from these studies shaped public health messaging early in the pandemic to suggest that patients with cardiac co-morbidities were at higher risk of adverse outcomes from COVID-19 infection. However, this notion has been subsequently challenged.

Investigators from two large registries (CAPACITY-COVID registry and LEOSS Study Group), which included 16,511 patients across 18 countries, assessed the association between different subtypes of cardiovascular disease (arrhythmia, conduction disease, atrial fibrillation [AF], coronary artery disease, heart failure [HF] and valvular disease) and in-hospital mortality in patients hospitalised with COVID-19. After multivariable analysis, only HF (New York Heart Association class III or IV) was found to confer a significantly higher risk of in-hospital mortality (relative risk 1.41).[7] This association between pre-existing HF and in-hospital mortality was also reported by Bhatt et al., who found that approximately 25% of patients with HF died during hospitalisation.[8]

It is unclear why there is a discrepancy between earlier and later data; however, one possible explanation is that limited testing capacity in the early days of the pandemic may have under-estimated the true prevalence of COVID-19, and hence milder cases were not diagnosed and captured in the observational studies.

Myocardial infarction

There is an established link between respiratory infections and the incidence of acute myocardial infarction (AMI). For example, patients who are affected by influenza virus or other respiratory infections have an increased hazard of AMI (OR 2.01). In addition, vaccination against influenza virus has been shown to reduce the incidence of AMI, further supporting the association between these two conditions.[9] From a pathophysiology perspective, this observation can be explained by a number of factors. Respiratory illness can lead to systemic inflammation, prothrombotic states, myocardial supply–demand mismatch, platelet activation, coronary vasoconstriction and endothelial cell dysfunction. These factors can lead to plaque rupture and thrombosis, with resultant myocardial injury. Therefore, it is not surprising that cohort studies have identified an increased risk of AMI after COVID-19 infection.

A self-controlled case series and cohort study from Sweden examined the temporal association between COVID-19 infection and AMI in 86,742 patients.[10] In the first week after infection, the relative risk of AMI was 8.44, which reduced to 2.56 in the second week and 1.62 for the third and fourth weeks following infection (risk ratios are lower when day 0 was excluded). Similarly, a nationwide, register-based, self-controlled case series from Denmark examined the short-term outcome of 5,119 patients with confirmed COVID-19 infection. It found that the incidence of AMI was five times higher in the first 14 days after diagnosis when compared to a control interval. The increased incidence of AMI remained statistically significant when extended to include cases occurring within 21 and 31 days from the index COVID-19 diagnosis, indicating a sustained period of enhanced risk.[11] Recent data have shown that COVID-19 recovered patients have persistently higher risk of incident myocardial infarction several months following recovery (hazard ratio [HR] 1.93 at a mean follow up of 8.5 months), though the risk reduces with time.[12]

Concurrent COVID-19 infection and myocardial infarction

Given the frequent occurrence of AMI and COVID-19 infection in most populations, it naturally follows that some patients will be affected by both conditions concurrently. This raises the question about the outcome of these patients, taking into account the virulence of SARS-CoV-2.

In a multi-centre observational study across 42 ST-elevation myocardial infarction (STEMI) care networks in Spain, investigators examined the outcome of patients presenting with STEMI during a period where there was COVID-19 community transmission.[13] Of 1,010 consecutive patients, 91 patients (9%) had COVID-19 infection. Patients with concurrent COVID-19 infection and STEMI were more likely to have HF on admission (31.9% vs 18.4%), cardiogenic shock post primary coronary intervention (PCI) (9.9% vs 3.8%), stent thrombosis (3.3% vs 0.8%) and cardiovascular (13.2% vs 5.1%) and all-cause mortality (23.1% vs 5.7%).

Further corroborating these findings is data from the North American COVID-19 STEMI registry,[14] which investigated the outcome of 230 patients with confirmed COVID-19 infection compared to 995 controls. Patients with COVID-19 and STEMI were more likely to present in cardiogenic shock or following cardiac arrest, but were less likely to have primary PCI as compared to age and sex-matched control patients. While door-to-balloon time was longer in those with COVID-19 infection, they were more likely to have no culprit lesions identified on invasive angiography. COVID-19 positive patients had longer intensive care and hospital lengths of stay, and the primary outcome of in-hospital

death, stroke, recurrent MI or unplanned revascularisation occurred in 36%, compared to only 4% in control patients, which was driven primarily by in-hospital mortality.

These above findings are not surprising when considering the observation that COVID-19 positive patients presenting with STEMI have greater infarct size, reduced left ventricular function, greater intracoronary thrombus burden, higher rates of cardiogenic shock, requirement for haemodynamic support and life-threatening arrhythmias.[5] Summarising these studies and others, a meta-analysis by Gharilbzadeh et al. found the pooled prevalence of mortality of COVID-19 patients with STEMI was just over 25%.[4]

Currently, recommended management of patients remains the same regardless of COVID-19 status—invasive coronary angiography and PCI to culprit lesions is considered first line for STEMI management, with fibrinolysis performed in cases where target time cannot be achieved. Thrombus aspiration can be utilised on a case-by-case basis for patients with high intracoronary thrombus burden, and case series have demonstrated the potential use of low-dose rivaroxaban in scenarios where no culprit lesion was found.[15] In patients with non-ST elevation acute coronary syndromes (NSTE-ACS), medical stabilisation and early angiography is recommended in high-risk cases, while non-invasive imaging can be considered in selected intermediate or low risk cases.[16]

Another important factor to consider is the organisation of hospital operations during a pandemic. In an analysis by Sofi et al., it was found that during the first peak of the pandemic, STEMI hospitalisations had reduced in countries with lower hospital bed availability but remained similar to previous levels in countries with greater hospital bed availability.[3] There was no evidence indicating that the stringency of lockdown measures made a difference to STEMI presentations. This pattern has been confirmed in a national New Zealand registry study by Chan et al. and other single centre studies,[17,18] noting that in the absence of widespread community transmission and low hospital occupancy of COVID-19 cases, there was no difference in hospitalisation for STEMI, whereas the rates of NSTE-ACS initially reduced during a national COVID-19 lockdown. As the burden of COVID-19 was low, the reduced hospitalisation for NSTE-ACS was likely in part the result of behavioural changes in response to public health messages, but a genuine reduction in NSTE-ACS was also possible. These epidemiological advantages are no longer applicable to New Zealand's current status.

Myocardial injury and myocarditis

Raised serum cardiac troponin levels are commonly observed in patients with COVID-19 and can reflect myocardial injury.[19] Similar to other viral respiratory infections, a raised troponin level is associated with adverse outcomes and in-hospital mortality in patients with COVID-19.[20] However, the link between troponin elevation and outcome is not uniform. For example, in a study across four Swiss centres, raised troponin levels were more commonly observed among patients hospitalised with influenza than those with COVID-19, yet COVID-19 patients had significantly higher 28-day mortality.[21] The exact cause of raised troponin levels in this setting may not always be clear, but potential causative mechanisms for myocardial injury in patients with COVID-19 have been described. For example, SARS-CoV-2 has been found in endomyocardial biopsies of some patients suspected of having myocarditis.[22] Furthermore, Puntmann et al. found that among patients recently recovered from COVID-19 infection, there was evidence of ongoing myocardial inflammation in about 60% of patients based on cardiac magnetic resonance imaging.[23] Despite these findings, only a small proportion of patients develop clinical pericarditis or myocarditis (0.2% as reported by the CAPACITY-COVID study), indicating that the myocardial inflammation seen on histology or imaging may be asymptomatic. Lastly, other biomarkers such as brain natriuretic peptide are also raised in some patients with COVID-19.[24] All of this underscores the need to investigate the underlying aetiology of raised biomarkers, if clinically appropriate, to guide appropriate treatment.

Routine screening for myocarditis in COVID-19 patients is not generally recommended except for those with supportive clinical features or evidence from clinical examination, electrocardiography or echocardiography. The best estimate for the incidence of myocarditis in patients with COVID-19 comes from a unique study performed by Daniels et al. In their cohort study of 1,597 patients with COVID-19, cardiac evaluation and magnetic resonance imaging was performed, and 37 (2.3%) were diagnosed with myocarditis, but this was subclinical in 28 out of 37 patients,[25] and this raises a question about the relevance of asymptomatic imaging findings. However, the presence of myocardial inflammation likely reflects a more aggressive disease course, which adds to the overall risk and clinical picture of the individual patient.

Arrhythmia

Arrhythmic complications of COVID-19 have been observed in several cohorts. These data are

best summarised in a study by Coromalis et al., who conducted a large retrospective analysis of 4,526 patients with COVID-19, across 12 countries, of whom 827 patients had been affected by incident arrhythmia.[26] It is noteworthy that most of these patients had no prior history of arrhythmia, indicating that this was a *de novo* phenomenon. Of the 827 patients, greater than 80% developed atrial arrhythmias, while the remainder developed ventricular arrhythmias (non-sustained ventricular tachycardia [VT], polymorphic VT/torsade de point, or ventricular fibrillation). Furthermore, 22% also developed bradyarrhythmia, antrio-ventricular (AV) block or ventricular pauses greater than 3 seconds. In this group, 5% underwent permanent pacemaker insertion, suggesting significant or persistent bradyarrhythmic events. Regional variation was noted, for example, patients from Asia had lower rates of incident AF (34% compared to the global incidence of 61%) but higher rates of bradyarrhythmia and AV block (43% compared to global incidence of 22%). Overall, only 51% of patients who developed arrhythmias survived to discharge from hospital, with slightly increased mortality risk for those who developed VT (37% survival to discharge).

Despite these observations, it is difficult to directly attribute incident arrhythmia to COVID-19 infection. In the above study, patients with arrhythmia were older (71 years, compared to mean age of 62.8 for the total cohort). Those patients who developed ventricular arrhythmias also had high rates of hypoxia, metabolic abnormalities, renal failure, and treatment with QT prolonging medications, and there was a subset that were treated with inotropic agents. All of these factors could contribute to a pro-arrhythmic milieu, and it is possible that the observation of *de novo* arrhythmia simply reflects a more aggressive disease course. It remains to be established whether SARS-CoV-2 can directly lead to the development of *de novo* arrhythmia.

The management of arrhythmias in patients with COVID-19 is similar to standard care advice.[16] In all cases, precipitating factors such as electrolyte imbalances should be corrected. For AF, beta-blockers and calcium channel blockers are recommended for rate control in hemodynamically stable patients, while intravenous amiodarone is recommended for patients with hemodynamic instability. Therapeutic anticoagulation is indicated for male patients with a CHA_2DS_2-VASc score >1 or female patients with a score of >2. Transthoracic echocardiography is recommended for assessment cardiac structure and function. For VT, therapeutic options include intravenous beta-blockers, lidocaine, amiodarone, and synchronised direct-current cardioversion. For ventricular fibrillation, asynchronous direct current defibrillation is indicated. Advanced therapies are reserved for patients with refractory ventricular arrhythmias, with options including temporary pacing, intubation, and extra-corporeal membrane oxygenation.

Severe incident bradyarrhythmias should be investigated with echocardiography or cardiac magnetic resonance imaging where appropriate. In patients with hemodynamic instability, chronotropic agents such as intravenous atropine and isoprenaline should be administered. A subset of patients may require temporary or permanent pacemaker implantation, and these are evaluated on an individual patient basis.

Venous thromboembolism (VTE)

COVID-19 has been associated with increased risk of venous and arterial thromboembolic events. The risk of incident events declines with time from the initial COVID-19 diagnosis, though it remains elevated for up to a year. Amongst 1.4 million patients from England and Wales who tested positive for COVID-19, when adjusted for age, sex and region, the HR for developing deep vein thrombosis (DVT) was 12 in the first week after COVID-19 diagnosis, declining to 2.6 at 27–49 weeks. Similar trends were observed for pulmonary embolism (PE) (adjusted HR 39 at 1 week, declining to 2.2 at 27–49 weeks) and arterial thrombosis (HR 27 at 1 week, and 1.9 at 27–49 weeks).[27] This is pertinent because patients with PE have high mortality rates (19%) compared to those with COVID-19 without PE.[28] It has been noted that COVID-19 patients with VTE have fewer classical risk factors, though they still suffer from high mortality rates. Given the propensity of COVID-19 patients to develop PE without DVT, *in situ* clot formation via disruption of the pulmonary circulation (due to endothelial damage, micro-embolism and angiogenesis) have been postulated as mechanisms to explain this difference.[29,30]

Guideline recommendations in hospitalised and critically ill COVID-19 patients suggest low molecular weight heparin as the first line agent for VTE prophylaxis, as per standard prophylaxis dosing.[31] Therapeutic heparinisation (low molecular weight heparin or unfractionated heparin) is recommended for the initial treatment of VTE, while direct oral anticoagulants or warfarin can be used for extended treatment. A minimum of

three months of anticoagulation is suggested for treatment. In patients already on anticoagulation presenting with recurrent VTE, higher dose low molecular weight heparin is recommended. Patients with confirmed PE who have obstructive shock or cardiopulmonary compromise, and who are at low risk for major bleeding, should be treated with thrombolysis. Mechanical thromboprophylaxis should be avoided in critically ill COVID-19 patients.

Heart failure

COVID-19 has been implicated in the development of *de novo* HF and in exacerbation of chronic HF.[32] *De novo* HF appears to be relatively uncommon, with observational studies providing estimates of 1.2%–2.5% of affected patients,[7,33] whereas the total combined incidence of *de novo* and acute decompensation of chronic HF was estimated to be 10% in one study.[34]

More importantly, patients with pre-existing HF represent a particularly high-risk group for adverse outcomes. As mentioned earlier, pre-existing HF is an independent risk factor for developing severe COVID-19 infection.[35] A large review by Bader et al. reported that patients who had HF and septic shock had mortality rates of 70–90%, compared to 20% in those with sepsis but without HF or cardiovascular disease.[32]

For patients with chronic HF, standard guideline recommendations regarding goal-directed medical therapy remain unchanged,[16] and emphasis is placed on preventing COVID-19 infection. This can be achieved with measures such as vaccination and use of telemedicine to reduce physical clinics visits where possible, as well as standard public health measures.

Long COVID

There is emerging evidence that a proportion of patients who develop COVID-19 have persistent symptoms after recovery from the index infection, termed “long COVID”. Numerous risk factors have been described, including female gender, belonging to an ethnic minority, socio-economic deprivation, chronic obstructive pulmonary disease, smoking, obesity and psychiatric conditions.[36] While fatigue appears to be the most common feature, cardiopulmonary symptoms are an important component of this syndrome, and there are wide-ranging estimates of their prevalence.[37] For example, separate cohorts have reported that six months after recovery, chest pain was reported by 5% and palpitations reported by 9% of survivors.[38] Autonomic symptoms are common, and while most patients do not demonstrate abnormal findings during tilt table testing,[39] cardiac symptoms should not be discounted, as imaging studies have provided evidence for cardiac abnormality in this group. For example, in one study of 534 patients who underwent cardiac magnetic resonance imaging at baseline, 6 months and 12 months after the onset of long COVID symptoms, there was evidence of cardiac impairment in approximately 20% of patients (ventricular dilatation or systolic dysfunction, reduced global strain, or elevated native T1 signals).[40] Therefore, the occurrence of cardiovascular symptoms in survivors of COVID-19 should be investigated as per usual standards of practice.

It should be stated that there is a paucity of data about the long-term outcome of COVID-19 survivors who suffer any of the aforementioned complications during the index illness. While it is reasonable to extrapolate treatment strategies from existing guidelines pertaining to each condition, it is not known whether cardiac phenomena observed during acute COVID-19 illness follow the expected natural history. A good example of this is the occurrence of *de novo* AF in patients with acute COVID-19 or similarly any other systemic illness. Clinical experience suggests that many of these patients may not necessarily develop recurrent AF after recovery, which obviates the need for rate, rhythm, and antithrombotic therapy.[41,42]

Conclusion

COVID-19 infection is associated with numerous cardiac complications, and the occurrence of these is often a negative prognostic indicator. Clinicians should be vigilant for the development of adverse cardiac events in hospitalised patients with COVID-19. Long COVID will possibly become an epidemic itself, and further research into its mechanisms and treatment strategies is needed. Vaccination against COVID-19 and public health measures remain key in curbing infection rates, and therefore risks of both short and long-term complications of COVID-19.

COMPETING INTERESTS
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Failure of SGLT-2 inhibitor in the context of new ileal conduit formation

Joel Almog, Shalu Jain, Phillip Pybass, Ankur Gupta

Sodium glucose co-transporter-2 (SGLT-2) inhibitors are being increasingly used in the management of diabetes mellitus for better cardiovascular and kidney outcomes. The common adverse effects mentioned in the literature include polyuria, genitourinary infections, hypotension, volume depletion and increased risk of euglycemic ketoacidosis.[1] It is advised to stop these drugs in the periprocedural period and to restart post-operatively only once the patient is eating and drinking normally or close to discharge from hospital.[2] We herein report an unusual clinical scenario where restarting SGLT-2 inhibitors was detrimental to the overall glucose control.

Case report

A 71-year-old male, with a background of type 2 diabetes mellitus, developed uncontrolled hyperglycaemia after radical cysto-prostatectomy and ileal conduit formation for high-risk (T1 high grade and CIS) bladder cancer. His anti-diabetic home medications, metformin 500mg twice daily and empagliflozin 10mg daily, were kept on hold during the peri-operative period. Periprocedural glucose control was done with short acting insulin. As per protocol, home doses of antidiabetic medications were reinitiated on post-operative day 2. Laboratory results reveal that despite increasing the dose of empagliflozin to 25mg daily, blood glucose remained uncontrolled (see Figure 1). Stopping empagliflozin and up-titration of metformin to 1000mg twice daily resulted in sustained normo-glycaemia. Moreover, ketonaemia started to develop (ß-hydroxybutyrate of 2.3) after increasing the dose of empagliflozin, thus providing further motivation to stop the empagliflozin. Renal profile, blood counts and lipid levels in both the pre-operative and post-operative periods remained largely unchanged (except for transient, anticipated post-operative changes) and have been included in Table 1 below.

Discussion

Empagliflozin, a SGLT-2 inhibitor, blocks the reabsorption of up to 90% of filtered glucose in the proximal convoluted tubule (PCT), thereby

Figure 1: Pre-, peri- and post-surgical serum glucose control (day 0 to day of surgery).

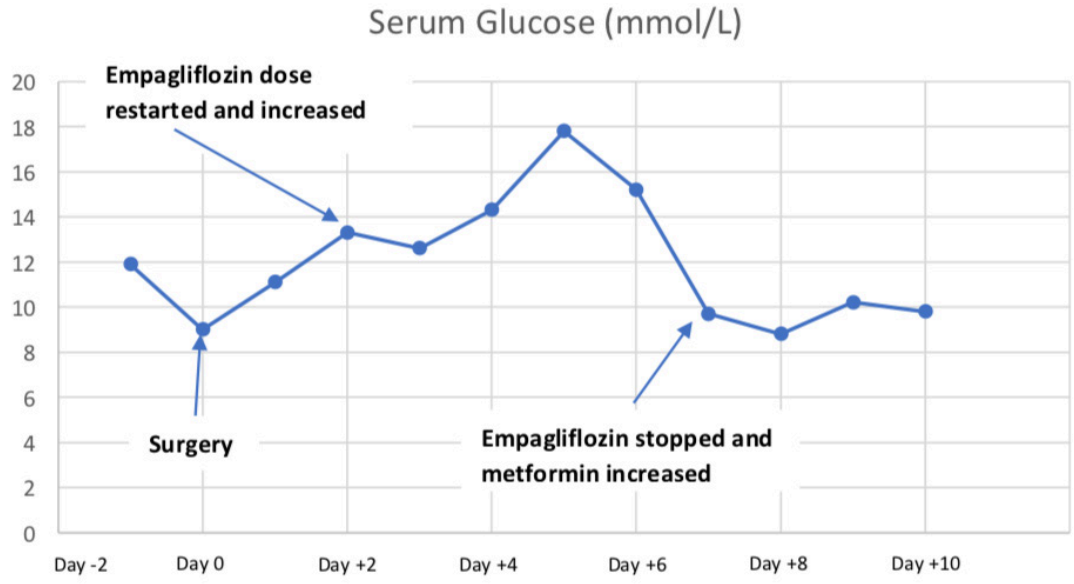

Table 1: Renal profile, blood counts and lipid levels.

	Pre-operative period	Post-operative period
Renal profile		
Creatinine	66umol/L	61umol/L
Urea	6.6mmol/L	5.2mmol/L
Sodium	136mmol/L	137mmol/L
Potassium	4.1mmol/L	3.9mmol/L
Calcium (adj)	2.52mmol/L	2.43mmol/L
Phosphate	1.2mmol/L	0.98mmol/L
Magnesium	0.75mmol/L	0.77mmol/L
Bicarbonate	23mmol/L	25mmol/L
Blood counts		
Haemoglobin	132g/L	107g/L*
White cells	9.6x10'9/L	16.2x10'9/L**
Platelets	202x10'9/L	331x10'9/L
Lipid levels		
T. Cholesterol	3.1mmol/L	3.6mmol/L
Triglyceride	2.2mmol/L	2.0mmol/L
cLDL	1.4mmol/L	2.0mmol/L
HDL	0.9mmol/L	0.8mmol/L

* Drop in haemoglobin most likely attributed to peri- or post-operative blood loss.
** Transient rise in WCC post-operatively.

increasing total urinary excretion of glucose.[3] This urinary glucose is then stored in the bladder until micturition occurs. In the setting of an ileal conduit, urine is stored in a section of ileum, which acts as an artificial bladder. Ileum has SGLT-1 transmembrane proteins which re-absorb the excreted urinary glucose, thereby minimising the effects of the SGLT-2 inhibitor. The enterocytes can upregulate Na-dependent glucose transport after exposure to glucose in a timeframe of a few minutes.[4] These intracellular transporters are recruited resulting in SGLT-1 appearance at the apical membrane. Moreover, intestinal glucose transporter (GLUT-2) also translocates to the apical surface in response to high intra-luminal glucose levels. This would enable SGLT-1-independent glucose uptake at high luminal glucose concentrations as postulated in our case. Furthermore, selectivity for SGLT-2 relative to SGLT-1 inhibition is 2,700-fold for highly selective empagliflozin.[5] Thus, empagliflozin induced glucosuria resulted in a positive feedback loop of more glucose resorption via the ileal conduit worsening hyperglycaemia in our case. An extensive literature survey did not yield any previous case reports on this topic.

Conclusion

In the setting of a new ileal conduit formation, prescribers should avoid highly selective SGLT-2 inhibitors like empagliflozin. This scenario could be an indication to use novel dual SGLT1/2 inhibitors like sotagliflozin and licogliflozin. More data would be required to further validate these results in this select group of individuals.

COMPETING INTERESTS
Nil.

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An Anatomist's Ode to His Love

NZMJ, 1923

I list as thy heart and ascending aorta,
Their volumes of valvular harmony pour,
And my soul from that muscular music has caught
New life 'mid its dry anatomical lore.

O rare is the sound when the ventricles throb;
In a systolic symphony, measured and slow,
While the auricle answers with rhythmical sob
As it murmurs a melody wondrously low.

Ah! thy cornea, love, has the radiant light,
Of the sparkle that laughs in a icicle's sheen;
And thy crystalline lens, like a diamond bright,
Thro' the quivering frame of thy iris is seen!

And thy retina, spreading its lustre of pearl,
Like a far-away nebula, distantly gleams.
From a vault of black cellular mirrors that hurl
From their hexagon angles the silvery beams.

Ah! the flash of those orbs is enslaving me still,
As they roll 'neath the palperbrae dimly translucent,
Obeying, in silencee, the magical will
Of the oculi motor, trochlear, abducent.

Sweet is thy voice as it sighingly swells
From thy dainty quivering chordæ vocales,
Or rings in clear tones thro' the echoing cells
Of the antrum, the ethmoid, and sinus frontales.

And stately the heave of thy maidenly breast
As the swell of the billow swift rolling to land,
And as soft the vesicular sigh in thy chest
As the moan of the ripple that ebbs o'er the sand.

But, alas, with many forebodings I pen
Anatomical verses, thy beauty to praise,
For I fear me my studies will never again
Bring the solace thy had in my happier days.

–"89", in *The Speculum.*