CLINICAL ISSUES: CARDIOVASCULAR DISEASE IN HEART FAILURE AND RHEUMATOID DISEASE

Special report from the World Congress of Internal Medicine, Cape Town, October 2018

Non-communicable diseases (NCDs), driven by the cardiovascular epidemic, account for 70% of deaths in developing countries. At the 2018 World Congress of Internal Medicine, hosted in Cape Town from 18 to 21 October, risk factors of lifestyle and environment proved a common thread in all fields of medicine. These factors play a role in cardiovascular disease (CVD) and the metabolic syndrome, as well as inflammatory illness; they also affect the interplay between these disorders. Expert presentations shared insights into and current opinion on the management of heart failure, cardiometabolic comorbidities in inflammatory and rheumatoid illness, CVD prevention and lifestyle interventions.

Heart failure management

Where are we at with heart failure management in 2018?

**KEY MESSAGES**

- Great strides have been made in recent decades in respect of treating heart failure (HF)
- Angiotensin-converting enzyme inhibitors (ACE-Is) are the cornerstone of treatment for HF with reduced systolic function
- There is no treatment that convincingly reduces morbidity and mortality in HF with preserved ejection fraction (HF-PEF)
- The increasing number of elderly patients with multiple comorbidities requires an increasing focus on the latter and a multidisciplinary approach
- Regular aerobic exercise improves functional capacity and symptoms in stable patients.

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Professor McDonagh observed that chronic HF is a big subject and that she would focus primarily on HF with reduced systolic function (HF-REF) as opposed to HF-PEF. HF-REF is classified as an EF <40%.

“We’ve come a long way but it’s taken a long time,” she said. Disease-modifying treatments only started to become available in the 1980s. Drugs include diuretics, ACE-Is, angiotensin II receptor blockers (ARBs), beta-blockers, ivabradine, sacubutril-valsartan and aldosterone antagonists. “Diuretics are still used as first-line therapy because they improve symptoms. However, we no longer use them in industrial-strength doses; we now use the smallest doses so as not to activate the renin-angiotensin-aldosterone system. While we can’t say they improve mortality, all other drugs are used against a background of loop diuretics and may not work in their absence.” The goal of therapy is to improve symptoms at the minimum dose to reduce congestion and achieve dry weight.

ACE-Is are the cornerstone of treatment for HF-REF, convincingly reducing morbidity, mortality and hospitalisation, while improving symptoms and cardiac function. Concordant results have been obtained in both HF and post-myocardial infarction trials. For the ACE-I-intolerant, ARBs have a smaller place.

Beta-blockers are established as second-line therapy. Once a patient is on an ACE-I plus beta-blocker and carefully titrated, spironolactone can be added, as it has been shown to reduce all-cause mortality and hospitalisation.

There is class 1A evidence in any guideline for ACE-Is/ARBs, beta-blockers and mineralocorticoid receptor antagonists (MRAs). If patients get symptomatically worse, despite the use of these agents, ivabradine can be introduced in those patients with heart rates >70.

The combination of an ARB (valsartan) and neprilysin inhibitor (sacubutril) (ARNI) is a relatively new treatment for HF. An ARNI is indicated in patients with ambulatory symptomatic HF-REF, a left ventricular ejection fraction (LVEF) ≤35%, elevated plasma natriuretic peptide levels and an estimated glomerular filtration rate (eGFR) ≥30ml/min/1.73m². Professor McDonagh cautioned, however, that there are some safety issues that need to be borne in mind when initiating this drug in clinical practice.

What about digoxin, the ‘original HF treatment’? It is neutral in respect of all-cause mortality but does reduce hospitalisation. However, there are challenges associated with its therapeutic range.

Turning to devices, Professor McDonagh observed that cardiac resynchronisation therapy is a life-saving treatment in patients with a wide QRS complex, but may be harmful in those without.1 The use of implantable cardioverter defibrillators is recommended as secondary prevention to reduce the risk of sudden death and all-cause mortality in patients who have recovered from a ventricular arrhythmia and are expected to survive for one year with good functional status. Their use should be limited to those with an EF <35% and avoided in patients with serious comorbidities such as cancer.

Where HF-PEF is concerned, there is no treatment that convincingly reduces morbidity and mortality. The findings of large trials have been disappointing. Diuretics are advised for symptomatic relief.

A bigger problem is the increasing number of older HF patients with multiple comorbidities; the mean age at presentation has increased to 77 years and the mean number of comorbidities, including chronic kidney disease (CKD), chronic obstructive pulmonary disease and diabetes, is 5.4. “All of these impact mortality and we need an increasing focus on these comorbidities,” observed Professor McDonagh.

“We have come a long way with regard to survival rates in HF-REF. The one-year mortality rate in clinical trials is now 8%.”
**Optimising diuretic therapy in HF**

**KEY MESSAGES**

- Diuretics improve the symptoms of HF, despite having no prognostic benefit
- Loop diuretics are most commonly used in HF
- They should not be given until perfusion and blood pressure (BP) are adequate
- Fluid and salt restriction are important
- If pharmacokinetic problems occur, increase the dose or consider intravenous (IV) therapy. If there are pharmacodynamic issues, increase the frequency and add a thiazide diuretic.

Diuretic resistance occurs when the diuretic response is diminished before the therapeutic goal of relief from congestion has been reached. “It is important to recognise congestion in order to relieve it and to ascertain whether perfusion is good or low. The latter is easy to determine, but congestion may not be obvious and is difficult to diagnose,” said Dr Klug.

Renal blood flow is similarly of paramount importance, as is the need for ultrasound of the chest to detect pulmonary oedema. Diuretics should not be given until adequate perfusion is established and BP is controlled. The goal of diuresis should be a minimum reduction of 5-10% of body weight. An increase in the creatinine level may be required to adequately relieve congestion.

Venous congestion plays an important role in worsening renal function and a central venous pressure (CVP) higher than 24 predicts worsening kidney function, regardless of systolic BP. There is also a link between inadequate perfusion and central venous congestion; and when both are present, they are associated with worse renal function. Patients with HF tend to have high levels of thirst. Fluid intake should nonetheless be restricted and excess fluid should not be given intravenously while in hospital.

There are three major types of diuretic: loop diuretics, thiazide diuretics and MRAs (potassium-sparing diuretics). The loop diuretics furosemide, bumetanide and torasemide are most commonly used in the treatment of HF. They have a venodilator action that precedes their diuretic effect. This is beneficial in congestive HF. “When treating critical illness, it’s important not to do harm, and as yet we have no good randomised trials on diuretic use in HF,” cautioned Dr Klug.

Diuretics do have symptomatic benefits - diminishing congestion, lowering left ventricular filling pressure and alleviating oedema and dyspnoea. However, their effectiveness is reduced by excess salt intake, underlying CKD, renal adaptation to diuretics and neurohormonal activation.

Patients who respond do better, and patients with persistent congestion have poorer outcomes. Dr Klug pointed out, however, that high doses of furosemide may worsen outcomes and increase mortality.

Diuretics act on the tubular surface of the cell, not the vascular surface. They are absorbed in the gastrointestinal tract and their bioavailability differs from the IV dose: 50% for furosemide, 90-100% for the other two. Diuretics are important organic acids and bind strongly to albumin. Many other drugs (aspirin, NSAIDs) compete with them for delivery to the tubular lumen, and it may be necessary to increase the oral dose to compensate for this. Switching to IV therapy is another way to overcome diuretic resistance.

Chronic therapy may lead to adaptation, with a diminished response over time (the ‘breaking phenomenon’) and distal convoluted tubule hypertrophy. Adding a thiazide to chronic loop diuretic therapy may bring about a synergistic response.

In principle always use the lowest dose, and adjust as the patient improves, given that increased doses and combination therapy can worsen renal function.

Concluding, Dr Klug reiterated that loop diuretics are the ones most commonly used in HF and are highly effective for addressing symptoms, despite no evidence of prognostic benefit. The
The management of anaemia in HF

**KEY MESSAGES**

- Anaemia increases the workload of the failing heart and is an important risk factor for morbidity (including kidney disease) and mortality.
- IV iron is currently the best treatment for anaemia in HF.

Anaemia (a loss of red cell blood mass) in the presence of HF indicates a poor prognosis. If found to be present, it is important to consider nutritional deficiencies, erythropoietin, inflammation, occult bleeding, bone marrow failure and idiopathic anaemia of ageing. “Hepcidin, a protein that is a key regulator of the entry of iron into the circulation, plays a central role. Hepcidin blocks the absorption of iron, so if we can reduce it, we can release more iron.”

HF is characterised by decreased myocardial function, abnormal loading and arrhythmia. In HF-REF, inflammatory markers that block the release of iron are important. These include tumour necrosis factor alpha (TNF-α), interleukins (ILs) and C-reactive protein (CRP). Anaemia increases the workload of the already failing heart and is an independent risk factor for morbidity and mortality.

Thirty-seven percent of HF patients have anaemia, putting them at risk for CKD. Fifty percent will have iron deficiency without anaemia and may present with fatigue long before they develop overt anaemia.

Blood transfusions are not advisable. Erythropoietin is also of questionable value as bone marrow is resistant to it and it has no effect on the inflammatory response. “All studies show that the best outcomes are achieved with IV iron, even in iron-deficient patients without anaemia.” Trials of anti-hepcidin therapy are ongoing, and the targeting of an anti-hepcidin pathway may be an alternative treatment in the future.”
Inflammatory and rheumatic disease

Cardiometabolic comorbidities in inflammatory and rheumatic diseases

**KEY MESSAGES**

- Cardiometabolic comorbidities are of concern in inflammatory arthritis
- Comorbidities differ between and within inflammatory disease and require different solutions
- The mainstay of treatment is to control inflammation and CVD risk factors
- Management must include lifestyle interventions.

**CVD**

The pathogenesis and pathophysiology of CVD differ between rheumatoid arthritis (RA) and spondyloarthritis (SpA). Increased cardiovascular mortality risk associated with RA has been ascribed to its carrying a higher inflammatory burden than SpA conditions. People with RA, psoriatic arthritis (PsA) and psoriasis are at increased risk of cardiovascular events.

The greatest increase in risk of RA-associated cardiovascular mortality is at a young age; with older age, risk reduces to almost normal population levels.\(^4,5\) Traditional risk factors such as lipid levels can be misleading and very hard to interpret in the face of inflammation, as cardiovascular risk factors may behave differently in RA (e.g. as CRP levels increase with increased inflammatory burden, circulating lipid levels decrease).\(^6\)

While real-life data show no difference in rates of myocardial infarction between those on TNF inhibitors compared to those on disease-modifying antirheumatic drugs (DMARDs), this is confounded by selection bias. Myocardial infarction risk in those who respond to TNF inhibition by six months is markedly reduced (66%) compared to non-responders.\(^7\) The CANTOS study\(^8\) has shown reduced CVD events using IL-1 inhibition with canakinumab; with the fall in CRP after a single dose of canakinumab the best predictor of benefit, confirming the causal link between inflammation and CVD, even in the general population.\(^9\)

In PsA, 80% of people have multimorbidity and 60% have at least two other conditions. All PsA outcomes worsen as the number of comorbidities increases, and patients are less likely to respond to biologics and other therapies.\(^10,11\)

The cardiovascular risk factors of hypertension, type 2 diabetes (T2DM) and obesity are all increased in PsA compared to psoriasis; and in psoriasis compared to the general population.\(^12\) Compared to RA, PsA shows only a slightly increased CVD risk, despite a far greater risk burden.

Increased risk of cerebrovascular events features across the SpA spectrum, probably related to increased hypertension in this group. There is a higher risk of hypertension with mild psoriasis compared to the general population and patients with severe psoriasis have a yet greater risk. PsA has the highest stroke risk in the psoriatic disease spectrum.\(^13\)

**Metabolic syndrome**

In psoriatic disease, risk for T2DM and metabolic syndrome increases in correlation to severity of disease. Risk for T2DM and obesity is almost doubled with psoriasis compared to the general population. Two-thirds of patients with PsA have...
metabolic syndrome by some definition, whereas only one-quarter to one-third of RA patients have metabolic syndrome.\textsuperscript{14,15}

Of note is that obesity itself is a risk factor for psoriatic disease. For every standard deviation increase in BMI, the risk of psoriasis increases by 20%. This dose response extends to risk of developing PsA, where a female with BMI >35 has a six-fold increased risk. Fat distribution is more predictive of cardiovascular risk than BMI; visceral fat, being more metabolically active, is of greater concern and waist circumference can be a useful surrogate measurement. Again, there is a dose response between weight and the likelihood of achieving minimal disease activity, with obese patients less likely to respond as well to therapy.\textsuperscript{16-18}

Patients with psoriasis are at greater risk of fatty liver disease (as part of the metabolic syndrome) than RA, with risk doubling further in PsA compared to psoriasis. As a consequence, methotrexate therapy in this group carries a far higher risk of liver impairment and is often not tolerated.\textsuperscript{19}

The complexity of PsA extends beyond the cardiovascular element. Other than inflammation, there is a metabolic drive that Dr Siebert considers to be part of the disease. He predicts that future therapies will be using metabolic drugs in tandem with immune-modulating agents.

Dr Siebert’s recommendations for best management of cardiovascular risk in inflammatory arthritis are to:

- Treat the inflammatory disease aggressively
- Measure BP
- Stop smoking
- Adjust CVD risk for RA and inflammatory arthritis using a risk calculator (QRISK-2, SCORE)
- Remember the lipid paradox (treat inflammation before worrying about lipids)
- Check for diabetes (particularly in PsA)
- Promote physical activity and healthy diet
- Implement weight management programmes for obese patients.

### Approach to spondyloarthritis

#### KEY MESSAGES

- SpA comprises a heterogeneous group of non-rheumatoid, phenotypically related conditions
- Effects of therapeutic agents differ between RA and SpA
- Effects of therapeutic agents differ within the SpA spectrum.

SpA comprises a group of phenotypically related (but heterogeneous) conditions with musculoskeletal and extra-articular features that are very different from those of RA.

The effects of some targeted therapeutic agents on RA and SpA conditions differ. Many agents ‘adopted’ from RA have worked well in treatment of non-rheumatoid conditions. Some DMARDs are effective for peripheral disease in the seronegative spectrum, but not for the spinal disease or enthesitis that often characterise the SpA conditions. TNF-inhibitors are largely effective across the board: psoriasis, PsA, uveitis, axial SpA, enteropathic arthropathy and inflammatory bowel disease (IBD). RA treatments that have been unsuccessful in SpA include rituximab, tocilizumab and sarilumab (no significant clinical benefit in ankylosing spondylitis (AS) despite reduction in CRP); and abatacept (modest response in PsA).

SpA conditions share common genetic and pathogenic features but differ in clinical response to specific immune-targeted interventions. Human trials targeting different cytokines suggest the existence of hierarchical networks of cytokines that define groups of chronic inflammatory diseases rather differently from the homogenous molecular disease pattern previously assumed.\textsuperscript{20}
IL-12/-23/-17A inhibitors

SpA conditions have shared (IL-23/-17, innate immunity) and disease-specific pathogenic pathways. Evidence from human studies indicates that IL-17 is a key cytokine in psoriasis. The IL-23/-17 pathway is key in PsA, AS and IBD.21,22

TNFα-inhibitors themselves reduce IL-17 activity. IL-23 has two sub-units, p19 and p40. The p40 sub-unit is shared with IL-12, so targeting p40 can inhibit both IL-12 and IL-23, although it is unclear whether or not this is better than inhibiting just IL-23 via p19. In RA, IL-23/-17A inhibition has no clear clinical efficacy. The response to therapeutic inhibition of these key cytokines differs across the SpA spectrum (Table 1).20

In psoriasis and PsA, IL-23 inhibitors (ustekinumab, guselkumab, adalimumab, risankizumab) and IL-17A inhibitors (secukinumab, ixekizumab) show good clinical efficacy, particularly in the skin where many patients achieve 95-100% skin clearance.

In AS, the IL-17A inhibitor secukinumab works well in both TNF-naive and TNF-exposed patients; however, IL-12/-23 inhibition has failed to demonstrate a clinical effect in the spine.

In contrast, in Crohn’s disease, the opposite holds true. Inhibiting IL-23 with ustekinumab is effective in TNF-inhibitor non-responders and TNF-naive patients; whereas inhibiting IL-17 appeared to aggravate the condition.

Table 1. Therapeutic cytokine inhibition in the RA and SpA spectrum
Adapted from Schett, 201320

<table>
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<th></th>
<th>TNF</th>
<th>IL-6R</th>
<th>IL-1</th>
<th>IL-12/23</th>
<th>IL-17A</th>
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<td>Rheumatoid arthritis</td>
<td>Good clinical efficacy</td>
<td>Good clinical efficacy</td>
<td>Moderate clinical efficacy, or preliminary data</td>
<td>Insufficient, or no clinical efficacy, or aggravating effect</td>
<td>Insufficient, or no clinical efficacy, or aggravating effect</td>
</tr>
<tr>
<td>Crohn’s disease</td>
<td>Good clinical efficacy</td>
<td>No data</td>
<td>No data</td>
<td>Good clinical efficacy</td>
<td>Insufficient, or no clinical efficacy, or aggravating effect</td>
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<tr>
<td>Psoriasis</td>
<td>Good clinical efficacy</td>
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<td>No data</td>
<td>Good clinical efficacy</td>
<td>Good clinical efficacy</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>Good clinical efficacy</td>
<td>Insufficient, or no clinical efficacy, or aggravating effect</td>
<td>No data</td>
<td>Good clinical efficacy</td>
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<tr>
<td>Ankylosing spondylitis</td>
<td>Good clinical efficacy</td>
<td>Insufficient, or no clinical efficacy, or aggravating effect</td>
<td>No data</td>
<td>Insufficient, or no clinical efficacy, or aggravating effect</td>
<td>Good clinical efficacy</td>
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“These drugs are telling us some really interesting things about our diseases…”
What lessons have we learned from IL-17 inhibition trials?

Even within the same patient there are tissue differences in response to therapies, implying functional cytokine hierarchical roles within different tissues. Figure 1 highlights cytokine pathways with demonstrable therapeutic effects in each discrete tissue based on responses in clinical trials. These comparisons are potential, rather than proven.23

Dr Siebert believes that in future there will increasingly be a move towards treating the molecular signature of the patient, rather than just the phenotype, with more head-to-head studies required in order to determine the best strategies.

Figure 1. Proposed notional emerging tissue cytokine hierarchy based on current clinical trial data23

Focus on CVD prevention

Hypertension management update

KEY MESSAGES

- Hypertension is the single biggest contributor to disease burden and mortality worldwide
- Awareness, treatment and control are worse in low-income countries
- Controlling BP with medication is the most cost-effective treatment strategy to prevent cardiovascular events
- Most patients will need two or more agents to achieve BP control
- Single pill combinations improve compliance.

Raised BP is the primary contributor to the global burden of disease and mortality. “It is the single biggest killer and the numbers are increasing year by year,” said Professor Poulter. “CVD affects one-third of adults worldwide, making it the largest epidemic known to mankind.”

Half the attributable CVD burden occurs at BP levels below what is classified as hypertension (≥140/90mmHg), and hence population-based strategies are required for prevention, not necessarily
pharmacological interventions. Risk factors include age, alcohol use, high salt and saturated fat intake, lack of exercise and being overweight.

The PURE study,²⁴ which looked at hypertension around the world, found that treatment and awareness rates get progressively worse as one moves from high- to low-income countries. “Globally, 46% of hypertensives don’t know that they have the condition, so greater awareness is critical.”

In the first ‘May Measurement Month’ campaign in 2017, an initiative of the International Society of Hypertension, 1.2 million individuals were screened. Over 250 000 had raised BP, of whom 100 000 were inadequately treated. In 2018, 1.5 million were screened; 220 000 were found to have untreated hypertension and 110 000 had inadequately treated hypertension. The two campaigns together identified and advised 580 000 people with raised BP and offered a unique opportunity to undertake global analyses.

“Controlling BP with medication is the most cost-effective treatment strategy to prevent cardiovascular events. Most people get treated once they know they’re hypertensive, but only one-third achieve control. Monotherapy is seldom sufficient, and most patients will require at least two drugs – but which two? Guidelines differ around the world, recommending either A+C (ACE-I/ARB plus calcium channel blocker), A+D (ACE-I/ARB plus diuretic) or C+D (calcium channel blocker plus diuretic).” Data are lacking as to which combination is optimal in different ethnic groups. Current US guidelines define hypertension as beginning at 130/80mmHg, while European guidelines have retained 140/90mmHg.

If two drugs prove inadequate to control BP, a third can be added for a combination of A+C+D. If that still proves inadequate, there is sufficient evidence to support the use of spironolactone as a fourth-line option.

Use of single pill combinations of two drug classes improves compliance and if compliance improves, BP improves. They’re also more cost-effective. “In addition, all patients should also be on a statin regardless of their cholesterol level, as this is about reducing overall cardiovascular risk. To prevent CVD effectively, we need to look at patients holistically and not at BP in isolation,” concluded Professor Poulter.

Residual cardiovascular risk – does it exist?

KEY MESSAGES

- Dyslipidaemia, especially LDL-cholesterol, plays a pivotal role in CVD
- There are some promising new treatments for cholesterol, namely the PCSK9 inhibitors and the ANGPTL3 inhibitors
- An LDL-cholesterol level of 1.8 mmol/l is the cut off-value for regression of atherosclerosis
- When treating dyslipidaemia, always bear inflammation and thrombotic risk in mind and treat concomitantly
- Early treatment is critical to minimise residual risk.

Despite major advances in the treatment of CVD, it remains a major killer responsible for 17 million deaths per annum. Hypertension, diabetes, smoking, obesity and dyslipidaemia all contribute, but the role of the latter, especially LDL-cholesterol, is pivotal. The statin trials, involving 170 000 people, have shown that for every 1mmol/l reduction in LDL-cholesterol, cardiovascular events are reduced by 29%. But ‘residual risk’ remains and tailored therapy is required to target cholesterol, inflammation and thrombotic risk.

“Statins and ezetimibe are effective and can bring about a 55-70% reduction in LDL-cholesterol, but those with familial hypercholesterolaemia are not reaching
target levels,” said Professor Raal. Newer drugs showing great promise are the PCSK9 inhibitors, whose journey from laboratory to clinical use has been rapid, and the ANGPTL3 inhibitors, currently under development. The PCSK9 inhibitor, alirocumab, has been shown to reduce LDL-cholesterol from baseline by almost 60%. The addition of evolocumab to statin treatment was shown to enhance the latter’s effects, further reducing atheroma volume.

Inflammation plays a key role in atherosclerosis, which is a chronic inflammatory process that in excess leads to a disease state. Experimental and clinical data suggest that reducing inflammation, even without affecting lipid levels, may reduce the risk of CVD. The CANTOS trial, using the monoclonal antibody canakinumab, dramatically reduced the inflammatory marker CRP, despite no change in LDL-cholesterol.

While lipids play a central role, it’s important always to bear inflammation and thrombotic risk in mind when treating dyslipidaemia. The combination of aspirin and a novel anticoagulant has been shown to reduce thrombotic risk by 25% in stable coronary artery disease.

Professor Raal concluded by underscoring that LDL-cholesterol is essential for the development of atherosclerosis, and that if we can remove this ‘ultimate cause’ we can effectively treat or even prevent the latter. Early treatment is very important, as treating the residual risk may well constitute doing ‘too little too late’.

How can we reduce premature CVD by 50% in a generation?

**KEY MESSAGES**

- Eighty percent of CVD and 90% of deaths are due to modifiable risk factors
- Eighty percent of deaths occur in low- and middle-income countries
- A polypill can reduce risk by >65%
- A combination of lifestyle measures and low-cost drugs, along with improved health systems, better vital statistics and greater involvement of non-physician health workers, will contribute to the halving of CVD within a generation.

Eighty percent of CVD deaths occur in low- and middle-income countries. In 1990, the figure was 12.7 million, and had risen to 17.3 million by 2013. While the age-specific death rate has in fact declined, the increase can be attributed to an increase in the size of the population and to ageing.

Several facts about CVD prevention are clear and irrefutable. Tobacco avoidance, lowering LDL-cholesterol by 1mmol/l (regardless of level) and lowering systolic BP by 10mmHg together reduce disease by 75%. Professor Yusuf cautions that tobacco usage is not a thing of the past, despite the worldwide decline in smoking and smoking-related deaths in recent decades; and that tobacco use will still kill one billion people in the course of this century. “Smoking cessation is therefore critical,” he said. “When it comes to BP, meta-analyses have shown that the higher the BP, the greater the benefits of reduction.”

Low- and middle-income countries generally have weaker health systems, and access to and affordability of treatment are often poor. Non-severe disease is picked up and treated earlier in wealthy countries, so fatalities are lower. It’s because treatment is poorer in poor countries that death rates are higher, not because of risk factors.

BP is easy to control, but at least two drugs are usually needed, and affordability is a major stumbling block. “The key is to make these drugs more affordable and available.” Eighty percent of hypertensives in India cannot afford the medications they need. “Guidelines are written for academics in rich countries and have limited value in poor countries.”
A polypill, comprising BP/cholesterol agents and aspirin, can reduce cardiovascular risk by >65%. But having the drugs isn’t enough. “We also need to deliver.” Professor Yusuf underscored the important role that non-physician health workers can play, as well as the importance of support from friends and family.

Addressing CVD is not only about medication. Lifestyle modification should entail tobacco avoidance, increased physical activity, reduced salt and alcohol intake, as well as dietary measures. “Diet is never a straight line and the data are not always clear. However, the Mediterranean diet does appear to lower cardiovascular risk, and high-fat diets also appear to be more beneficial than high-carbohydrate ones.” High carbohydrate intake is a major problem in low- and middle-income countries.

Professor Yusuf feels that investing in education, more than any other policy, is key to improving global health. “Eighty percent of CVD and 90% of deaths are due to modifiable risk factors. A combination of lifestyle measures and low-cost drugs, along with improved health systems, better vital statistics and greater involvement of non-physician health workers will go a long way towards halving CVD within a generation,” he concluded.

Exercise is the best medicine!

**KEY MESSAGES**

- In South Africa, NCD deaths outnumber combined deaths from communicable diseases and injury/violent death.
- Physical inactivity is the modifiable risk factor associated with the biggest risk reduction for all-cause mortality and chronic disease
- Risk of primary cardiac arrest transiently increases during vigorous exercise, although habitual vigorous exercise is associated with an overall decreased risk
- Medical clearance is appropriate in the presence of existing CVD, symptoms of CVD, pregnancy, chronic disease and in the presence of any acute illness.

In 2018, more than 65% of deaths globally were due to NCDs, with this figure expected to rise exponentially in the coming decade. CVD, cancer, chronic lung disease and diabetes comprise 82% of all NCD deaths. In Africa, there is a 21% probability of dying of one of these four main NCDs; in South Africa, NCD deaths outnumber combined deaths from communicable diseases and injury/violent death.

Professor Schwellnus refers to the ‘eight deadly sins’ of NCDs, broadly categorising them as daily choice risk factors (tobacco, harmful use of alcohol, unhealthy diet, physical inactivity) and metabolic or physiological risk factors (obesity, elevations in BP, blood sugar and certain types of blood fats). Adherence to healthy lifestyle behaviours could reduce the risk for death from all causes. Specific combinations of lifestyle risk behaviours may be more harmful than others, suggesting synergistic relationships among risk factors. The greater the number of risk factors that can be reduced, the more substantial the reduction in risk of dying, even in the presence of pre-existing disease or older age.

Physical inactivity is the modifiable risk factor associated with the biggest risk reduction for all-cause mortality and chronic disease (Figure 2). Risk reduction for all-cause mortality is 32% with physical activity vs 14% with statins; 33% vs 25%, respectively, for CVD mortality; and risk reduction for transition from pre-diabetes to diabetes is 58% with physical activity vs 31% with metformin.
How does physical activity affect health?

A dose response to amount of exercise is associated with longer life expectancy across a range of activity levels and BMI groups. Individuals who are regularly physically active have a 30-45% lower risk of early death. Additional health benefits include a lowered risk of up to:

- 35% for coronary heart disease and stroke
- 50% for T2DM
- 50% for colon cancer
- 20% for breast cancer
- 83% for osteoarthritis
- 68% for hip fracture
- 30% for falls among older adults
- 30% for depression
- 30% for dementia.

How much physical activity is recommended?

SEMLI guidelines recommend:
1. One hundred and fifty minutes of moderate- to high-intensity endurance physical training per week, with each session lasting 30 minutes or longer.
2. Strength and balance training 2-3 times per week.

Exercise in patients with existing disease

Reducing risk of injury is part of responsible promotion of physical exercise (Table 2). There is the risk of a medical complication occurring during an exercise session. Life-threatening and minor medical complications are associated with high-intensity exercise; and the ‘unmasking’ of a pre-existing underlying disease may occur. “The exercise prescription should match the patient profile,” advises Professor Schwellnus.

During moderate- to high-intensity training, many organ systems are challenged by the physiological response to exercise. An incorrect exercise prescription may, for example, precipitate a cardiac arrest or sudden death. This exercise paradox has risk of primary cardiac arrest transiently increased during vigorous exercise, although habitual vigorous exercise is associated with an overall

Table 2. Preventing exercise-related injuries.

- If injured already, get expert help
- Start training slowly, progress gradually
- Perform an adequate warm-up/stretching
- Develop normal muscle strength, balance and optimal neuromuscular control
- Use the correct sports equipment
- Be aware of correct exercise technique (biomechanics)
- Use protection (strapping, bracing) if appropriate
- Realise the value of optimal nutrition
- Psychological status is linked to injury risk
- Consider lifestyle/behaviors (e.g. smoking).
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decreased risk of primary cardiac arrest.\textsuperscript{31}

For moderate- to high-intensity exercise, Professor Schwellnus recommends medical clearance in males older than 45 years and females older than 55 years with more than one risk factor for CVD. Medical clearance is also appropriate in the presence of any existing CVD, any symptoms of CVD (chest pain, dizziness, shortness of breath), pregnancy, use of prescription medication for chronic disease, known underlying chronic disease, development of symptoms during exercise, concerns about the safety of the exercise and in the presence of any acute illness.

References


