Hypertension

Innovative treatment in barbershops by pharmacists

In the USA, non-Hispanic black men have the highest hypertension-related mortality. This is associated with lower rates of antihypertensive treatment and worse control than in black women. A trial in 52 barbershops enrolled regular patrons with uncontrolled hypertension to either (i) intervention with a structured laptop interview, automated in-shop blood pressure (BP) recording and treatment by a specialty-trained pharmacist according to a stepwise treatment protocol (calcium channel blocker + angiotensin converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB), followed by indapamide, followed by spironolactone) or (ii) referral to the client’s primary care physician.

In six months, the intervention group recorded an average 27mmHg fall in systolic pressure vs. 9.3mmHg in the group treated by their primary care physicians. Compared to controls, the net BP reduction in the treated group was 21.6/14.9mmHg and the intervention was safe and well tolerated. This study result suggests that community-based programmes of this nature can offer a more effective means of obtaining blood pressure control than usual primary care management.

Type 2 diabetes

The CANVAS trial found a reduction in cardiovascular (CV) death, myocardial infarction (MI) or stroke in high risk patients with diabetes who were treated with canagliflozin, the sodium-glucose co-transporter 2 (SGLT2) inhibitor, when compared to placebo. The primary endpoints, hospitalisation for heart failure and progression to albuminuria, were reduced by canagliflozin whereas the incidence of limb amputation was increased (6.3% vs. 3.4% per 1000 patient years). There was however no evidence of proportional differences in this increased risk between patients with and without heart failure. There may be a greater benefit in those patients with a history of heart failure than in those without (HR 0.61 vs 0.87).
Acute coronary syndromes

SECURE-PCI randomised 4000 patients with acute coronary syndrome (ACS) who were to undergo percutaneous coronary intervention (PCI) within 7 days, to either atorvastatin 80mg before and 24 hours after PCI or placebo (1:1). Both groups received atorvastatin 40mg daily immediately thereafter. Eventually, 65% got PCI, 8% coronary artery bypass grafting (CABG) and fully 27% were treated medically. There were no differences in outcome at 30 days. However, in the group who got PCI there were significant differences in major adverse cardiac events (MACE) (6.0% vs. 8.2%, p=0.02) and MI (3.6% vs. 5.2%, p=0.04) that manifested early in the trial in favour of initial treatment with the high dose statin (Figure 1).3

Dual antiplatelet therapy in ACS

In an open-label, randomised multicentre trial, SMART-DATE evaluated 6-month vs. 12-month or longer dual antiplatelet therapy (DAPT) after PCI in patients with ACS. This study from Korea included 2700 patients loaded with aspirin and a P2Y12 inhibitor (79% clopidogrel) and treated with a drug-eluting stent for either 6 months or 12 months or longer (Figure 2). No difference in major adverse cardiac and cerebrovascular events (MACCE) was found between 6-month and 12-month DAPT over the entire period of 540 days. However, a landmark analysis from 180 days indicated a non-significant difference in MACCE in favour of prolonged treatment (Figure 3). MI was reduced from 1.8% to 0.8% with prolonged DAPT, with an increase in Bleeding Academic Research Consortium (BARC) Type 2-5 bleeding from 2.7% to 3.9%. The investigators concluded that in the absence of an excess bleeding risk, DAPT should be continued for 12 months post-ACS.

Figure 1: Outcome of SECURE-PCI trial3

Figure 2: Study design of SMART-DATE
Secondary prevention

**LDL-cholesterol lowering**

Alirocumab is a fully human antibody against proprotein convertase subtilisin kexin 9 (PCSK9), which is known to be safe and well tolerated and produces substantial and sustained reduction in LDL-cholesterol (LDLc) and other atherogenic lipoproteins. Possibly the most significant contribution at the meeting was the presentation of the ODYSSEY Outcomes trial of alirocumab (75mg or 150mg subcutaneously fortnightly) vs. placebo in 19000 patients following an ACS: approximately 35% ST elevation myocardial infarction (STEMI), 48% non-STEMI and 17% unstable angina. South Africa contributed more than 500 patients.

A very high proportion of patients received guideline recommended treatment with aspirin (96%), a P2Y12 inhibitor (87%), an ACEi or ARB (78%) and a beta blocker (85%). Revascularisation had been performed in 72% of patients.

Patients were enrolled an average of 2.6 months after their ACS if their LDLc exceeded 1.8mmol/L on statin treatment, or non-HDL cholesterol exceeded 2.6mmol/L, or apolipoprotein B was greater than 80mg/dL on maximized statin treatment (the latter two groups constituted only 6.3% of the enrolled patients). Uncontrolled hypertension, heart failure, left ventricular dysfunction, and an eGFR<30 were amongst the exclusion criteria. The PCSK9 inhibitor was given in addition to high dose atorvastatin or rosuvastatin (89% of patients), or maximally tolerated doses of statin therapy or, in the 1% of patients who were not on lipid-lowering therapy, alirocumab was given alone. Ezetimibe with or without statin was used in 3%. All patients were treated for a minimum of 2 years; the median treatment duration was 2.8 years.
The on-treatment LDLc target was 0.6 to 1.2mmol/L (Figure 4). Significantly, patients whose LDLc fell below 0.4mmol/L were withdrawn from treatment. After 4 months of treatment, the PCSK9 inhibitor had reduced the average LDLc to 1.0mmol/L compared to 2.4mmol/L in placebo-treated patients. Over 48 months, the on-treatment LDLc in the intention-to-treat group rose to 1.7mmol/L and to 1.4mmol/L in the on-treatment group. The rise is not ascribed to attenuation of effect or the presence of neutralising antibodies but due to (i) progressive reductions in statin dose, (ii) protocol mandated withdrawal of treatment in those whose LDLc had fallen below 0.4mmol/L, who were then treated on placebo (7.7%), and (iii) premature discontinuation of treatment (14%). A similar upward drift of LDLc levels to 2.6mmol/L was also observed in the placebo-treated group.

The trial found a 15% reduction (an absolute risk reduction of 1.6%) in the combined endpoint of coronary heart disease (CHD) death, non-fatal MI and hospitalisation for unstable angina. Of the components of the endpoint, only CHD death failed to reach statistical significance. However, it was noted that all-cause deaths and ischaemia-driven coronary revascularisations were significantly impacted. An intriguing finding was that there was a larger (around 30%) beneficial effect in the tertile of patients whose baseline LDLc was greater than 2.6mmol/L at baseline. Other than injection site reactions, there was no concern about the safety of this treatment over the 4 years of the study.

Along with the previously reported FOURIER study with evolocumab, ODYSSEY Outcomes reinforces the evidence that reducing LDLc to very low levels is safe and affords additional benefit in preventing the dire sequelae of acute coronary syndromes and stable chronic coronary artery disease. However, the PCSK9 inhibitors are presently very expensive (US$ 14000 p.a.). With an absolute risk reduction of 1.6% in ODYSSEY, 63 patients need to be treated for 4 years to reduce one endpoint. This currently represents a treatment cost of US$ 3.5 million (ZAR 42 million). Therefore, despite the overall benefit derived in both trials, it will be incumbent on clinicians to focus PCSK9 inhibitor treatment on patients who will derive the greatest “bang for their buck”. Unfortunately, the present evidence base is insufficient to guide such decisions. We must await publication of the ODYSSEY Outcomes results before drawing any further conclusions.
Anti-inflammatory therapy

Canakinumab is a human monoclonal antibody targeting interleukin 1-beta. The CANTOS trial enrolled patients with prior MI and an hs-CRP>2mg/l. Canakinumab 150mg subcut 3-monthly reduced CV death, MI and stroke compared to placebo. Similar results were observed in patients with and without diabetes. Canakinumab did not reduce the incidence of new diabetes. Canakinumab reduced major adverse vascular events in patients with an eGFR<60; greater benefit was seen in those where hs-CRP fell <2mg/l.

Anti-coagulation strategies

The COMPASS trial enrolled over 27000 patients with stable atherosclerotic disease either present in two territories or with two additional risk factors, who were then randomised to taking aspirin alone, rivaroxaban 5mg bd alone or aspirin plus rivaroxaban 2.5mg bd. The group receiving the combination had a significant reduction in CV death, MI and stroke compared to either of the other two groups. The combination also reduced all-cause mortality by 15% (3.4% vs. an average of 4.1% in the other two groups). There was an increase in major bleeding of around 1% with the combination therapy. The incidence of MACE was higher in the subgroup of 7470 patients with peripheral arterial disease. In an evaluation of some 7000 COMPASS patients with lower extremity peripheral artery disease, the combination of rivaroxaban 2.5mg bd and aspirin significantly reduced major adverse limb events (MALE) by 43% vs. aspirin alone. The importance of strategies to reduce MALE is underlined by the in-trial observation of a 22.9% incidence of amputation and 8.7% mortality at 1 year.

Value of a wearable cardioverter-defibrillator post-MI

Patients with a reduced ejection fraction following an acute MI are at risk of sudden death. Current guidelines recommend the implantation of a cardiac defibrillator in such patients 3 months after the event. Therefore, the utility of a wearable cardioverter-defibrillator commencing within 7 days of hospital discharge after an MI in patients with an LVEF<0.35 was investigated in the VEST trial. Patient compliance was not as good as expected as the device was worn for an average of only 14 hours/day. Sudden cardiac death and ventricular tachyarrhythmic death were not significantly reduced although a reduction in overall mortality was seen in compliant patients.

Coronary intervention

CYP2C19 polymorphisms inhibit responsiveness to clopidogrel. ADAPT-PCI evaluated physician responses to CYP2C19 genotyping following PCI. The genotype was made available to the physician within hours of the PCI. The investigators found that while the genotype result partially influenced the prescribing of prasugrel or ticagrelor in preference to clopidogrel, the results were not universally implemented. Genotyping did not influence the prescription of either prasugrel or ticagrelor when the patient was already receiving either of these agents.

Heart failure

In the INDIE study, inhaled nebulized inorganic nitrate failed to improve the exercise capacity of patients with heart failure with preserved ejection fraction (HFpEF) over 4 weeks. A substudy of the US participants in the TOPCAT trial of spironolactone in HFpEF found that sudden cardiac death (SCD) accounted for 19% of the fatalities in the trial. Male sex and insulin-treated diabetes conferred a higher risk of this outcome. Spironolactone did not influence the incidence of SCD.
Protection against cardiotoxicity in breast cancer patients

HER2 positive breast cancer patients were evaluated for protection against trastuzumab-induced cardiotoxicity provided by either lisinopril or carvedilol compared to placebo. Patients were divided into two cohorts depending upon whether they also received anthracycline or not. Whereas no benefit was derived in the group receiving trastuzumab only, both lisinopril and carvedilol provided equivalent protection against cardiotoxicity in the anthracycline-treated cohort (Table 1).

Table 1: Conclusions of cardiotoxicity study

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<th>Conclusion</th>
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<td>In patients with HER2 positive breast cancer treated with trastuzumab, the cardiotoxic events were similar on placebo, lisinopril or carvedilol with comparable treatment interruptions</td>
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<td>Both lisinopril and carvedilol were effective in preventing cardiotoxicity in patients who were treated with both trastuzumab and anthracyclines</td>
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<td>•</td>
<td>Cardiotoxicity associated with trastuzumab superimposed on prior or current exposure to anthracyclines can be prevented with lisinopril or carvedilol</td>
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<td>In high risk patients who may benefit from an anthracycline-containing regimen, the use of lisinopril or carvedilol is justified and should be considered to offset cardiotoxic events from the use of anthracyclines in combination with trastuzumab.</td>
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Atrial fibrillation

In the mSToPS screening study, remote monitoring using a wearable ECG patch in patients >75 years of age, or in males over 55 or females over 65 who had a prior cerebrovascular accident, heart failure, diabetes, hypertension or obstructive sleep apnoea; detected new atrial fibrillation (AF) within 120 days in 5.1% vs. 0.6% in those not monitored. Approximately 7% of AF episodes lasted <5 minutes. The investigators recognised that the significance of these short episodes of AF requires greater clarification in respect of the stroke risk.

Aortic stenosis

The Danish NOTION trial compared the 5-year outcomes in surgical aortic valve replacement (SAVR) vs. transcatheter aortic valve replacement (TAVR) in patients >70 years of age with severe aortic valve stenosis. 139 TAVR patients were compared to 135 SAVR patients. 100% were followed up for 5 years. All-cause mortality, MI and stroke were similar in the two groups. AF occurred more frequently with SAVR whereas pacemaker implantation was more frequent with TAVR. Stroke and transient ischaemic attack (TIA) were numerically greater amongst TAVR patients, as were aortic valve re-intervention and valve endocarditis. Though prosthetic opening area was greater and the mean gradient lower with TAVR, mild and moderate aortic regurgitation were more common. New pacemaker implantation after TAVR was associated with an increase in mortality.

Non-cardiac surgery – myocardial injury

Myocardial injury after non-cardiac surgery (MINS) may be manifested as a clinical MI or a rise in hs-troponin. MINS is estimated to affect more than 8 million adults worldwide and is associated with an increase in CV events and death over the succeeding 2 years. In the MANAGE (management of myocardial injury after non-cardiac surgery) trial 1754 patients with MINS within the last 35 days were randomised to dabigatran 110mg bd or placebo starting an average of 5 days after their event (South Africa contributed 187 patients). 91% of patients had not had
ischaemic symptoms. Significant percentages of these patients were treated on secondary preventive therapies including antiplatelet agents, ACEi or ARB, beta blockers and statins. Permanent study drug discontinuation was high (46% in the dabigatran treated group) predominantly due to patient request. Dabigatran reduced the primary efficacy outcome of vascular death, nonfatal MI, non-haemorrhagic stroke, peripheral arterial thrombosis, amputation and symptomatic venous thromboembolism by 28% (Figure 6 and Table 2). The rate of life-threatening and critical organ bleeding was no different between dabigatran and placebo. There was a numerical increase in lower GI tract bleeding with dabigatran.

### Table 2. Conclusions of MANAGE trial

- Patients who have MINS are at substantial risk of major vascular complications and death
- Clinicians do not recognise the majority of MINS in the absence of routine post-operative troponin measurement
- Among patients with MINS, dabigatran 110mg bd resulted in a lower incidence of major vascular complications when compared to placebo.
References


2. Rådholm K, Fitger G, Perkovic V, et al. Canagliflozin and Heart Failure in Type 2 Diabetes: Results from the CANVAS Program (Canagliflozin Cardiovascular Assessment Study). *Circulation* 2018; Mar 11. doi:10.1161/CIRCULATIONAHA.118.034222


