ACC Annual Meeting 2022 Conference Review™

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In this review:

Abbreviations used in this review:

ACS = acute coronary syndromes; **AF** = atrial fibrillation; **BP** = blood pressure; **CV** = cardiovascular; **ED** = emergency department; **EF** = ejection fraction; **FXI** = factor XI; **HCM** = hypertrophic cardiomyopathy; **HDL/LDL** = high-/low-density lipoprotein; **HF** = heart failure; **MI** = myocardial infarction; **NYHA** = New York Heart Association; **SGLT** = sodium glucose cotransporter; **SRT** = septal reduction therapy.

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Welcome to this review of ACC 22,

the American College of Cardiology's annual meeting, which attracted thousands of CV professionals, some who attended in person and others virtually, for debate and discussion regarding practice-changing science and innovations in cardiology. Among the many informative presentations, this Conference Review's expert commentator, Phil Aylward, has selected ten for inclusion, focussing mainly on results from important clinical trials, which we hope you will find interesting and helpful in your everyday practice.

As with all our reviews, your feedback and comments are greatly appreciated.

Kind Regards,

Dr Janette Tenne

Editor

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Mavacamten as an alternative to surgical septal myectomy or alcohol ablation in patients with severely symptomatic obstructive hypertrophic cardiomyopathy

Presenter: Desai MY, on behalf of the VALOR-HCM investigators

Summary: In the VALOR-HCM trial, adults with obstructive HCM (hypertrophic cardiomyopathy) were randomised to receive mavacamten (a targeted inhibitor of cardiac myosin) starting at 5mg once daily with titrations at weeks 8 (2.5mg, 5mg or 10mg) and 12 (2.5mg, 5mg 10mg or 15mg; n=56) or placebo (n=56) once per day added to maximally-tolerated medical therapy. Compared with placebo, a significantly smaller proportion of mavacamten recipients met the composite primary endpoint of patient decision to proceed with or guideline eligibility for SRT (septal reduction therapy) at 16 weeks (17.9% vs. 76.8% [p<0.0001]); mavacamten recipients also had significantly better outcomes for the secondary endpoints of improvement in NYHA functional class and changes in postexercise left ventricular outflow tract gradient, Kansas City Cardiomyopathy Questionnaire clinical summary score, N-terminal prohormone of brain natriuretic peptide level and troponin I level. Mavacamten recipients had more nausea and rash, but less nonsustained ventricular tachycardia. There were no treatment discontinuations for left ventricular EF ≤30%, serious cases of congestive HF or syncope, or deaths.

Comment: The VALOR-HCM trial studied mavacamten, a targeted myosin inhibitor, that reduces the number of actin myosin cross bridges and reduces excess contractility in patients with severe HCM such that they had been referred for SRT. The result was outstanding. In the treatment arm after 16 weeks of treatment, the number of patients fitting the guideline for SRT was reduced to 18% compared with 77% in the control arm. The assessments were simple clinical and echo parameters. There were no safety signals, although it was of short duration and these are being followed in the EXPLORER-HCM trial. Discussion of the trial raised the concept that as well as excess hypertrophy, there is excess (hyper-) contractility. Mavacamten is not yet approved for clinical use but is being assessed by the US FDA soon.

Reference: Session 408 – Late-Breaking Clinical Trials Deep Dive I; 408-03

SODIUM-HF: study of dietary intervention under 100 mmol in heart failure

Presenter: Ezekowitz JA, on behalf of the SODIUM-HF investigators

Summary: The open-label SODIUM-HF trial randomised adults receiving optimally tolerated medical therapy for HF (NYHA class II–III) to a low-sodium diet (<1500 mg/day; n=397) or usual care (n=409); the trial was terminated early following a review on futility by the data monitoring committee, an assessment of trial operational feasibility and the impact of the COVID-19 pandemic. There was no significant difference between the low-sodium and usual care groups for the composite clinical outcome of all-cause mortality and CV-related hospitalisations or ED visits at 12 months (hazard ratio 0.89 [95% CI 0.63–1.26]) or for 6-minute walk distance, although there were modest, significant improvements in Kansas City Cardiomyopathy Questionnaire score and NYHA class for the low-sodium group.

Comment: Low-sodium diets have been a standard recommendation for patients with HF but with little evidence. This study compared a low-sodium diet with a standard diet and recommendations about salt intake in patients with class II–IV HF. There were four Australian sites, and 20% of the patients came from Australia or New Zealand. The primary endpoint of all-cause death, CV hospitalisations or CV ED visits was neutral with a slight but not significant increase in mortality. There were observed improvements in some measures of quality of life, but it was noted that the patients were unblinded. There was no change in NYHA class or 6-minute walk distance. Advice for low-sodium diet should not be a standard recommendation for patients with HF.

Reference: Session 402 – Joint American College of Cardiology/Journal of the American College of Cardiology Late-Breaking Clinical Trials: 402-11

Magnitude and duration of effects of a short-interfering RNA targeting lipoprotein(a)

Presenter: Nissen SE, for the APOLLO Study Investigators

Summary: Adults without known atherosclerotic CV disease and a lipoprotein(a) level ≥150 nmol/L were randomised to receive single subcutaneous doses of SLN360 (a silencing RNA targeting *LPA* gene-specific mRNA) 30mg, 100mg, 300mg or 600mg or placebo in the phase 1 APOLLO trial; each ascending dose was started 150 days after the one before, with six participants receiving that dose and two receiving placebo in each dose cohort. SLN360 administration was associated with lowering of lipoprotein(a) levels of ≤98%, with >70% and >80% reductions persisting for 150 days after the 300mg and 600mg doses, respectively. The higher doses were also associated with reductions in LDL cholesterol and apolipoprotein B levels by 20–30%. No major safety issues were reported, although there were low-grade, transient, dose-dependent injection-site reactions. Further details of the study have been published in JAMA.

Comment: The APOLLO trial was a small phase 1 trial to assess the dose effect and safety of a silencing RNA that reduces the levels of lipoprotein(a). There's increasing interest in lipoprotein(a), in part because treatments are becoming available. Twenty percent of the population have elevated levels of lipoprotein(a), and these are associated with premature atherosclerosis and aortic valve calcification. Lipoprotein(a) has a Kringle-like structure similar to plasminogen and contains inflammatory lipoproteins, and can be thought of as both atherogenic and thrombogenic. In the study, levels were reduced by 98% and 91% immediately after one subcutaneous injection of the respective top two doses, and remained at 81% and 71% at 5 months. There were no safety issues, but there were only 32 volunteers. However, the concept would be twice-yearly injections. This agent and others will obviously need further development, and the whole concept of lowering lipoprotein(a) will need a large outcome study.

Reference: Session 413 – Late-Breaking Clinical Trials Deep Dive II: 413-03

Effects of alirocumab on coronary atherosclerosis assessed by serial multimodality intracoronary imaging in patients with acute myocardial infarction

Presenter: Räber L, on behalf of the PACMAN AMI investigators

Summary: Patients with acute MI were randomised to receive 52 weeks of subcutaneous alirocumab 150mg (n=148) or placebo (n=151) every 2 weeks started within 24 hours of percutaneous coronary intervention, added to rosuvastatin 20mg, in the PACMAN-AMI trial. Compared with the placebo group, the alirocumab group had greater reductions in atheroma volume (primary endpoint; –2.1 vs. –0.9 percentage points [p=0.001]), mean LDL cholesterol level at week 52 (–84.8% vs. –50.7%), maxLCBI$_{4mm}$ (lipid probability at the 4mm with maximal lipid load of a vessel; –79.4 vs. –37.6mm [p=0.006]) and mean macrophage angle (–26.0° vs. –16.0° [p<0.001]), and a greater increase in minimal fibrous cap thickness (62.7 vs. 33.2µm). The two groups had similar any and serious adverse event rates.

Comment: PACMAN-AMI assessed the early use (within 24 hours) of the PCSK9 inhibitor alirocumab compared with standard of care in patients with ACS. The endpoint was various measures of plaque stability in the nonculprit arteries at 52 weeks. Most patients were statin-naïve (over 80%) and all were put on 20mg of rosuvastatin. The LDL cholesterol level fell to 0.6 mmol/L in the alirocumab arm and 1.9 mmol/L in the placebo arm. All the parameters of plaque stability were significantly better in the treatment arm, and the benefit appeared better as LDL cholesterol level got lower than 1.0 mmol/L. This trial reinforces that the lower the LDL cholesterol level, the better. It suggests that our target LDL cholesterol level in Australia in ACS patients should be lowered – currently still 1.8 mmol/L compared with 1.4 mmol/L in Europe – and the new targets should be as low as 1.0 mmol/L. It does not mean all patients should get a PCSK9 inhibitor straight away, but maybe the CCU protocol should be high-dose statin and ezetimibe.

Reference: Session 408 – Late-Breaking Clinical Trials Deep Dive I: 408-15

Long term effect of renal denervation on blood pressure reduction in patients on antihypertension medications

Presenter: Mahfoud F, on behalf of SPYRAL HTN-ON MED Investigators

Summary: Three-year outcomes from the SPYRAL HTN-ON MED trial were reported in this presentation; the trial had randomised hypertensive patients to radiofrequency renal denervation (n=38) or a sham procedure (n=42) added to stable BP-lowering medications; 13 participants from the sham control group crossed over to the renal denervation group between study years 2 and 3. The BP benefit reported with renal denervation over the sham procedure at 6 months (–6.3 vs. –1.6mm Hg [p=0.004]) persisted out to 36 months (–18.7 vs. –8.6mm Hg [p=0.004]), independent of antihypertensive pharmacotherapy. There were no safety issues recorded. This long-term analysis of the SPYRAL HTN-ON MED trial has now been published (Lancet 2022;399:1401–10).

Comment: This trial looked at 3-year outcomes of renal nerve ablation on levels of BP in hypertensive patients. The original 6-month results have been published. Renal nerve ablation has had a chequered history with initial enthusiasm and then dampening of expectations. This is a well-done study with sham procedures. There was one site in Australia. BP was significantly lower in the ablated group whether assessed by office or 24-hour measurement ~10mm Hg, there were fewer drug titrations in the treated group and 83% compared with 42% had a BP <140mm Hg systolic. The concept from this trial is that renal nerve ablation is one of the treatments for hypertension as well as the usual pharmacological and lifestyle measures. It will be interesting to see if it is widely taken up.

Reference: Session 411 – Featured Clinical Research III: 411-08

Multicenter, randomized, active comparator-controlled, double-blind, double-dummy, parallel group, dose-finding phase 2 study comparing the safety of the oral FXIa inhibitor asundexian with apixaban in patients with atrial fibrillation

Presenter: Patel MR, on behalf of the PACIFIC-AF Investigators

Summary: The phase 2 PACIFIC-AF study randomised patients with AF to receive the oral small molecule FXIa inhibitor asundexian 20mg (n=251), asundexian 50mg (n=254) or apixaban (n=250) once per day for 12 weeks. The primary safety endpoint was bleeding events, for which there were fewer than expected overall. The cumulative incidence ratio for asundexian (pooled) versus apixaban for major bleeding or clinically relevant nonmajor bleeding was 0.33 (90% CI 0.09–0.97; there were no major bleeds reported), for minor bleeding it was 0.47 (0.28–0.83), and for all bleeding it was 0.42 (0.26–0.67). The full trial report has now been published (Lancet 2022;399:1383–90).

Comment: This phase 2 trial assessed the safety of asundexian, an FXI inhibitor. FXI is part of the clotting cascade and amplifies thrombin. There is evidence from knockout animals and humans with genetic absence that inhibition will prevent pathological clotting but not prevent necessary clotting, i.e. will not increase bleeding, described as the holy grail of antithrombotic therapy. A number of compounds are in development. Two doses of asundexian were compared with apixaban in patients with AF. FXI levels were almost completely inhibited by the active agent. Bleeding events were rare and less than anticipated, so it was difficult to demonstrate a difference, but they were numerically lower with asundexian than with apixaban. Another advantage is that this is a once a day oral drug. The drug is moving forward for development in AF, MI and stroke.

Reference: Session 407 – Featured Clinical Research II: 407-08

Bentracimab immediately and significantly reverses the antiplatelet effects of ticagrelor in older people

Presenter: Bhatt DL

Summary: After receiving aspirin and ticagrelor for 48 hours, healthy volunteers were randomised to receive bentracimab (PB2452; n=154) or placebo (n=51) in this phase 2b trial to assess the investigational agent's ability to reverse the effects of ticagrelor. Compared with placebo, bentracimab resulted in a significant lower minimum percentage inhibition of P2Y12 reaction units within 4 hours (p<0.0001), with the effect evident as early as 5–10 minutes, robust across subgroups and without apparent rebound platelet activation. There were no thrombotic events or deaths recorded.

Comment: This study evaluated the effect of the ticagrelor reversal agent bentracimab on measures of platelet reactivity in older patients, aged 50–80 years. Ticagrelor is the commonly used P2Y12 receptor inhibitor in patients with ACS. Up to now there has been no way of reversing it; blood transfusion does not work. If a patient presents bleeding on ticagrelor it provides a major clinical dilemma. In this study rapid (within minutes) near complete reversal of platelet function was obtained without any significant side effects. However, there were only 150 patients treated with bentracimab. For me the main interest has been the discussion – some think that if there is a reversal agent, it gives ticagrelor an advantage over other platelet inhibitors. Although this agent use has been seen to be in acute bleeds, some cardiologists saw its possible use to reverse the effects when a patient needs to undergo an invasive procedure, and particularly if after loading for ACS, they need to go to cardiac surgery. Currently such patients wait a number of days and occupy scarce hospital beds. The agent is being tested in more numbers in the REVERSE-IT trial.

Reference: Session 403 – Featured Clinical Research I: 403-10

Antihypertensive therapy for mild chronic hypertension improves pregnancy outcomes

Presenter: Tita A

Summary: In the pragmatic multicentre CHAP trial, women (<23 weeks' gestation) with mild chronic hypertension were randomised to a BP goal of <140/90mm Hg using standard first-line antihypertensive agents for pregnancy (n= 1208) or a control group in whom antihypertensive therapy was only started if BP was ≥160/105mm Hg (n=1200), and were followed for 34 weeks. Compared with the control group, a smaller proportion of the active treatment group experienced a primary outcome event (pre-eclampsia with severe features, medically indicated preterm birth at <35 weeks' gestation, placental abruption or fetal/neonatal death; 30.2% vs. 37.0% [p<0.001]) and a similar rate of small-for-gestational-age birthweight below the tenth percentile for gestational age (11.2% vs. 10.4% [p=0.56]). Pre-eclampsia with severe features occurred in 23.3% and 29.1% of the active treatment and control groups, respectively, and fetal/neonatal death occurred in 3.5% and 4.3%.

Comment: This study assessed the benefit of treating pregnant women with mild chronic hypertension. This is a controversial area, with previous suggestions it may be negative for the foetus. The study was open-label and patients were randomised to an active arm to get BP down to <140/90mm Hg using the common BP treatments in pregnancy labetalol or nifedipine, or a control group where they were not treated unless their BP went above 160/105mm Hg. The active arm did better even though the BP difference was only 3mm Hg. The endpoints included maternal and neonatal outcomes. This suggests there should be more aggressive treatment of mild chronic hypertension of pregnancy. There was discussion about whether this would have long-term benefits, as pregnancy hypertension is now known to be a significant risk factor for late CV events.

Reference: Session 408 – Late-Breaking Clinical Trials Deep Dive I: 408-12

A cluster-randomized pragmatic trial aimed at improving use of guideline directed medical therapy in outpatients with heart failure

Authors: Ghazi L et al.

Summary: Adult outpatients with HF with reduced EF (n=1310) were randomised by provider (69% physicians, 31% advanced practice providers) to receive an electronic best practice alert or no alert at the time of an outpatient visit. For providers assigned to the intervention, a best practice alert was triggered when opening an order entry module, information was provided on current left ventricular EF, BP, heart rate, serum potassium and creatinine levels and estimated glomerular filtration rate, and recommendations for all four medication classes were displayed, with missing classes highlighted along with allergies and links to an order set with missing medications and indications. Compared with controls, participants assigned to the alert arm were more likely to have increases in: i) the number of guideline-directed medical therapy classes prescribed at 30 days (25.7% vs. 18.7% [p=0.03]; number needed to treat per alert), with a significant increase seen for β-blockers (5.8 vs. 2.9% [p=0.007]), but not renin-angiotensin-aldosterone system inhibitors (7.7% vs. 7.0% [p=0.22]), mineralocorticoid receptor antagonists (7.6 vs. 5.3% [p=0.20]) or SGLT-2 inhibitors (9.8% vs. 7.5% [p=0.41]); ii) the dose of current guideline-directed medical therapy medications or start of a new class (36.2% vs. 26.2% [p=0.010]). There was no significant between-group difference for 30-day ED visits or hospitalisations, or for safety outcomes. Among providers, 79% of those who received alerts agreed or strongly agreed that the best practice alert was helpful for improving guideline-directed medical therapy.

Comment: This study looked at the utility of alerts in the medical record to improve prescription of guideline therapy in patients with HF. The guidelines had the now-standard four mandated therapies including SGLT-2 inhibitors. The alerts would come up automatically if/when the medical record opened. The trial was a cluster randomisation trial. Around a quarter (25.7%) of the patients in the alert arm increased the number of classes of drug they were on, compared with 18.7% in controls, and 36.2% had a dose increase versus 26.2% in controls. These type of reminders are clearly beneficial, and other prompts, e.g. messages, also improve management. They would have value in many areas of cardiology. Unfortunately, many of the electronic records in the Australian environment do not have this facility, and there is the problem of multiple records at hospitals, private practices and GPs.

Reference: Session 406 – Joint American College of Cardiology/New England Journal of Medicine Late-Breaking Clinical Trials: 406-12

Effect of vupanorsen on non-high-density lipoprotein cholesterol levels in statin-treated patients with elevated cholesterol

Presenter: Bergmark B, for the TRANSLATE-TIMI 70 Investigators

Summary: Adults receiving stable statin therapy for non-HDL cholesterol levels ≥100 mg/dL and triglyceride levels 150–500 mg/dL (n=286) were randomised to receive vupanorsen (second-generation antisense oligonucleotide targeting hepatic ANGPTL3 [angiopoietin-like protein] mRNA) at dosages ranging from 80mg every 4 weeks to 160mg every 2 weeks or placebo in the TRANSLATE-TIMI 70 trial. There were significant placebo-adjusted decreases in non-HDL cholesterol levels of 22.0–27.7% (p<0.001) in all seven vupanorsen dosage groups, along with improvements in other lipid parameters at certain dosages, although improvements in apolipoprotein B levels were modest. However, vupanorsen recipients frequently experienced injection-site reactions, including recall reactions, higher monthly doses were associated with liver enzyme level increases, and there were dose-related increases in hepatic fat fraction.

Comment: TRANSLATE-TIMI 70 was a phase 2b trial of vupanorsen, an antisense oligonucleotide targeting hepatic ANGPLT3. The aim was to assess the effect of increasing dosages of vupanorsen on non-HDL cholesterol level. Non-HDL cholesterol level was lowered significantly as were triglyceride levels, but there was little effect on LDL cholesterol level, which raised concerns as to how much benefit there would be. Unfortunately also there were significant side effects at the injection site and in the liver. The drugs development has been discontinued. It reinforces the difficulty of developing new treatments and how agents may fall over at relatively late stages.

Reference: Session 405 – Joint American College of Cardiology/ Journal of the American Medical Association Late-Breaking Clinical Trials: 405-08

Independent commentary by Phil Aylward AM *MA (Oxon) BM, BCh, PhD, FRCP, FRACP, FACC, FCSANZ*

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He has a long standing interest in incorporating new trial data into clinical practice.

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