Cardiology Practice Review™

Making Education Easy

Issue 19 - 2022

In this issue:

Abbreviations used in this review:

ACC = American College of Cardiology
ESC = European Society of Cardiology
IDSA = Infectious Diseases Society of America
SCAI = Society for Cardiovascular Angiography and Interventions
TGA = Therapeutic Goods Administration

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Welcome to the 19th issue of Cardiology Practice Review.

This Review covers news and issues relevant to clinical practice in cardiology. It will bring you the latest updates, both locally and from around the globe, in relation to topics such as new and updated treatment guidelines, changes to medicines reimbursement and licensing, educational, medicolegal issues, professional body news and more. And finally, on the back cover you will find our COVID-19 resources for Cardiologists and a summary of upcoming local and international educational opportunities including workshops, webinars and conferences.

We hope you enjoy this Research Review publication and look forward to hearing your comments and feedback.

Kind Regards,

Dr Janette Tenne
Editor
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Clinical Practice

IDSA: Management of drug interactions with nirmatrelvir/ritonavir (Paxlovid®)

The Infectious Diseases Society of America (IDSA) has published a resource for clinicians on the management of drug interactions with nirmatrelvir/ritonavir, which is used for treating mild-to-moderate COVID-19 in patients at high risk for severe disease. Given coformulation with ritonavir as a pharmacokinetic booster, there is potential for drug interactions. Severe interactions, along with potential interactions with drugs used in cardiology, are highlighted below.

- Among the top 100 prescribed drugs, only two have interactions so severe that nirmatrelvir/ritonavir should be avoided altogether: **rivaroxaban** and **salmeterol** (as contained in Seretide and other preventers). Concomitant administration with rivaroxaban may increase bleeding, while concomitant administration with salmeterol may increase cardiac effects.
- Most **statins** should be held for the 5 days that a patient is on nirmatrelvir/ritonavir due to potential for increased toxicity, and for a further 5 days afterwards.
- Due to potential for increased bleeding, patients on **apixaban** 2.5 mg should avoid nirmatrelvir/ritonavir, whereas those on a 5 mg or 10 mg dose should reduce the dose by 50% until 3 days after nirmatrelvir/ritonavir.
- **Calcium channel blockers** can be continued if tolerated, but reduced if the patient has low blood pressure (amlodipine, nifedipine, diltiazem and verapamil) or bradycardia (diltiazem and verapamil).
- Patients on **clopidogrel** who have had coronary stenting should avoid nirmatrelvir/ritonavir for 6 weeks due to the risk of increased clotting.
- Nirmatrelvir/ritonavir has unpredictable effects on INR, therefore patients on **warfarin** should have INR monitored for dose adjustment.
- No dose adjustment is required for patients on **valsartan**, but consider reducing the dose if there is a risk of hypotension.

https://tinyurl.com/jahzus9b

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SARS-CoV-2 infection and associated cardiovascular manifestations and complications in children and young adults: A scientific statement from the American Heart Association

Cardiovascular complications are uncommon for children and young adults after COVID-19 disease or SARS-CoV-2 infection, according to a scientific statement from the American Heart Association. However, infection can lead to arrhythmias, myocarditis, pericarditis, or multisystem inflammatory syndrome (MIS-C).

The statement describes what has been learned about how to treat, manage, and prevent cardiovascular complications associated with COVID-19 in children and young adults, and calls for more research on short- and long-term cardiovascular effects.

Epidemiology

The latest evidence indicates that children usually have mild symptoms from SARS-CoV-2 infection. In the US, as of February 24, 2022, children under 18 years of age have accounted for 17.6% of total COVID-19 cases and about 0.1% of deaths from the virus. In addition, young adults, ages 18-29 years, have accounted for 21.3% of cases and 0.8% of deaths from COVID-19.

As with adults, children with comorbidities such as chronic lung disease or obesity and those who are immune compromised have a higher risk of hospitalisation, ICU admission, and death due to COVID-19. The evidence for the risk of severe COVID-19 in children and young adults with congenital heart disease is less clear, with some studies suggesting a slightly increased risk of severe COVID-19.

Clinical presentation

Regarding cardiovascular complications of COVID-19 in children, arrhythmias have included ventricular tachycardia and atrial tachycardia, as well as first-degree atrioventricular block. Although arrhythmias generally resolve without requiring treatment, prophylactic antiarrhythmics have been administered in some cases, and death due to recurrent ventricular tachycardia in an adolescent with hypertrophic cardiomyopathy has been reported.

Elevations of troponin, electrocardiographic abnormalities, including ST-segment changes, and delayed gadolinium enhancement on cardiac MRI have been seen in those with myocardial involvement. Although death is rare, both sudden cardiac death and death after intensive medical and supportive therapies, have occurred in children with severe myocardial involvement.

In a large retrospective paediatric case series of SARS-CoV-2-associated deaths in individuals under 21 years of age, the median age at death was 17 years and 63% were male. Of those who died, 86% had a comorbid condition, with obesity (42%) and asthma (29%) being the most common. But the report concludes that "although children with comorbidities are at increased risk for symptomatic SARS-CoV-2 infection compared with healthy children, cardiovascular complications, severe illness, and death are uncommon."

Multisystem inflammatory syndrome in children

Children and some young adults may develop MIS-C, a relatively rare but severe inflammatory syndrome generally occurring 2-6 weeks after infection with SARS-CoV-2 that can affect the heart and multiple organ systems. In the first year of the pandemic, more than 2600 cases of MIS-C were reported to the US Centers for Disease Control and Prevention, at an estimated rate of 1 case per 3164 cases of SARS-CoV-2 infection in children, with MIS-C disproportionately affecting Hispanic and Black children.

As many as 50% of children with MIS-C have myocardial involvement including decreased left ventricular function, coronary artery dilation or aneurysms, myocarditis, elevated troponin and BNP or NT-proBNP, or pericardial effusion. Acute-phase reactants, including C-reactive protein, D-dimer, ferritin, and fibrinogen, can be significantly elevated in MIS-C, neutrophil/lymphocyte ratio may be higher, and platelet counts lower than those with non–MIS-C febrile illnesses.

Fortunately, the outcome of MIS-C is generally good, with resolution of inflammation and cardiovascular abnormalities within 1-4 weeks of diagnosis. However, there have been reports of progression of coronary artery aneurysms after discharge, highlighting the potential for long-term complications. Death resulting from MIS-C is rare, with a mortality rate of 1.4%-1.9%.

Compared with children and young adults who died of acute SARS-CoV-2 infection, most of the fatalities from MIS-C were in previously healthy individuals without comorbidities. The authors recommend structured follow-up of patients with MIS-C because of concern about progression of cardiac complications and an unclear long-term prognosis.

The statement notes that the first-line treatment for MIS-C is typically intravenous immunoglobulin (IVIG) and patients with poor ventricular function may need to have IVIG in divided doses to tolerate the fluid load. Supportive treatment for heart failure and vasoplegic shock often requires management in an ICU for administration of inotropes and vasoactive medications. Antiplatelet therapy with low-dose aspirin is considered in patients with coronary artery involvement, and anticoagulation is added, depending on the extent of coronary artery dilation.

The statement notes that two doses of an mRNA COVID-19 vaccine can decrease the risk of MIS-C by 91% among children 12-18 years of age.

Prognosis and sports clearance

On returning to sports, data suggest it is safe for young people with mild or asymptomatic COVID-19 to resume exercise after recovery from symptoms. For those with more serious infections additional tests are recommended including cardiac enzyme levels, electrocardiogram, and echocardiogram, before returning to sports or strenuous physical exercise.

Vaccine-associated myocarditis

Myocarditis and pericarditis associated with the mRNA COVID-19 vaccine presents as chest pain and high troponin levels typically 2 to 6 days after vaccination. In a series of 63 patients ≤21 years of age with myocarditis temporally associated with the COVID-19 vaccine, the mean age was 15.6 years, 92% were male, all had an elevated troponin, 7% had significant arrhythmias, 14% had decreased left ventricular systolic function (ejection fraction, 45%–54%), and 88% had evidence of myocarditis on cardiac MRI. At mean follow-up of 35 days, 86% of patients had recovered; follow-up was not available in the remaining 14%. Treatment is mainly supportive with oral anti-inflammatory medications, although IVIG, steroids, and colchicine have been used.

For every 1 million doses of the mRNA COVID-19 vaccines in males ages 12-29 years (the highest risk group for vaccine-associated myocarditis), it is estimated that 11,000 COVID-19 cases, 560 hospitalisations and six deaths would be prevented, whereas 39-47 cases of myocarditis would be expected.

https://tinyurl.com/2p93hcy4

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Established CVD[1,2]

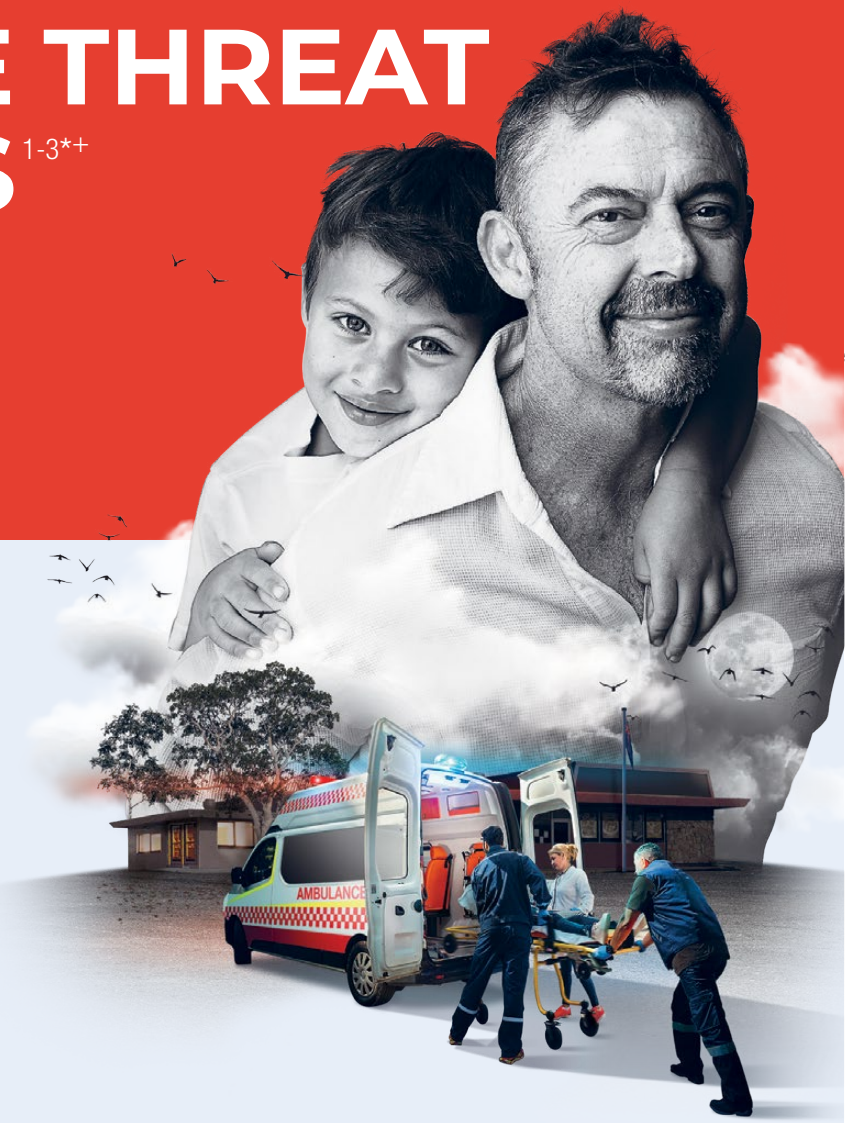
AMGEN
Cardiovascular

CONTROL LDL-C IN TRIPLE THREAT PATIENTS[1-3*+]

*1. LDL-C >2.6 mmol/L,[2]

2. despite optimised statin† and ezetimibe‡ therapy,[2§]

3. with ≥1 other CV risk factor (see PBS criteria)[2]



help prevent their next Triple Zero[3#]

†When Repatha (evolocumab) is added to optimised lipid-lowering therapy: 59% mean LDL-C reduction vs placebo at week 48 (95% CI: 58-60), p<0.001.[3]
#The RRR with Repatha for the primary endpoint (the composite of CV death, MI, stroke, hospitalisation for UA, or coronary revascularisation) vs placebo was 15% (HR, 0.85; 95% CI: 0.79-0.92; p<0.001). ARR: 2% and NNT 50 at 36 months.[3]
†Maximum recommended or tolerated dose of atorvastatin or rosuvastatin according to the approved Product Information for ≥12 consecutive weeks. ‡For at least 12 consecutive weeks.
§In conjunction with dietary therapy and exercise.

Repatha safety profile comparable to control;[1,3] evaluated across >35,000 patients in clinical trials, where >18,000 received Repatha and the most common adverse events occurring at an incidence of ≥2% and more frequently than any other control group were nasopharyngitis, upper respiratory tract infection, influenza, diarrhoea and dizziness.[1]

PBS Information: Authority Required. Non-familial and familial hypercholesterolaemia. Criteria apply for certain patient populations. Refer to PBS Schedule for full Authority Required information.
Refer to full Product Information before prescribing; available from Amgen Australia Pty Ltd, Ph: 1800 803 638 or at www.amgen.com.au/Repatha.PI. For more information on Repatha® or to report an adverse event or product complaint involving Repatha,® please contact Amgen Medical Information on 1800 803 638 or visit www.amgenmedinfo.com.au.

Repatha® (evolocumab)

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Abbreviations: ARR = absolute risk reduction; CI = confidence interval; CVD = cardiovascular disease; HR: hazard ratio; LDL-C = low-density lipoprotein cholesterol; MI = myocardial infarction; NNT = number needed to treat; RRR = relative risk reduction; UA = unstable angina. **References:** 1. Repatha (evolocumab) Approved Product Information. www.amgen.com.au/Repatha.PI. 2. Pharmaceutical Benefits Scheme. Available at: www.pbs.gov.au. 3. Sabatine MS *et al. N Engl J Med* 2017;376:1713-1722.
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SCAI guidelines for the management of patent foramen ovale

The Society for Cardiovascular Angiography and Interventions (SCAI) has published the first evidence-based guidelines for the management of patent foramen ovale (PFO).

The guidelines panel agreed on 13 recommendations to address variations on five clinical scenarios. Key recommendations address patient selection for PFO closure in the prevention of recurrent PFO-associated stroke, including populations not usually enrolled in randomised controlled trials, and settings where PFO closure might help in the prevention of other outcomes such as migraine headaches and decompression illness.

Key *conditional* recommendations for patients WITHOUT a prior PFO-related stroke are:

- Avoid the routine use of PFO in patients with chronic migraines, prior decompression illness, thrombophilia, atrial septal aneurysm, transient ischaemic attack, or deep vein thrombosis.
- Consider PFO closure in patients with platypnoea-orthodeoxia syndrome with no other discernible cause of hypoxia or systemic embolism in whom other embolic causes have been ruled out.

Key recommendations for patients WITH a prior PFO-related stroke are:

- For patients between the ages of 18 and 60 years, PFO closure is *strongly* recommended rather than antiplatelet therapy alone, whereas this recommendation is *conditional* for patients 60 years or older.
- For patients with atrial fibrillation who have had an ischaemic stroke, PFO closure is *conditionally* recommended against.
- In patients with thrombophilia on antiplatelet therapy and not anticoagulation therapy and who have had a prior PFO-associated stroke, PFO closure is *conditionally* recommended rather than antiplatelet therapy alone.
- The guidelines make no recommendation on PFO closure based on how much time has passed since the previous stroke, due to a lack of evidence.

Key recommendations for percutaneous PFO closure plus lifelong anticoagulation versus anticoagulation alone in adults with a prior PFO-associated stroke are:

- Patients who require lifelong anticoagulation because of recurrent DVT or recurrent pulmonary emboli or thrombopenia should have their PFO closed (*conditional* recommendation).

In an editorial accompanying the published guideline, the authors support the recommendations which help highlight and clarify the expanding list of potential indications for PFO closure. They note that the guidelines panel's strong recommendations are for indications supported by randomised controlled trials and that conditional recommendations are based on panellists' experience and observational data. The guidelines place a heavy emphasis on shared decision making with patients.

https://tinyurl.com/a9zjeb52

https://tinyurl.com/hcj3tbsj

The increasing role of rhythm control in patients with atrial fibrillation: *JACC* state-of-the-art review

Atrial fibrillation (AF) is the most common adult arrhythmia and poses a substantial burden on patients and health care services. Increasing evidence supports early rhythm control for most patients with recently diagnosed AF as well as for those who are symptomatic. A paradigm shift is evolving in favour of rhythm control rather than rate control for patients with new-onset AF.

The following are key points to remember about the increasing role of rhythm control in patients with AF, recently published in *Journal of the American College of Cardiology*.

Current AF management

Management of AF comprises three areas summarised in the "ABC" scheme of the 2020 European Society of Cardiology AF guidelines; "A" for anticoagulation/avoid stroke, "B" for better symptom control using rate and rhythm management, and "C" for therapy of concomitant cardiovascular conditions.

Key trials (PIAF, AFFIRM, RACE, AF-CHF, STAF, and J-RHYTHM) have demonstrated few significant differences in endpoints between rhythm- and rate-control strategies. In AFFIRM and RACE, there was a trend towards a higher mortality for rhythm control compared with rate control. Consequently, initial treatment is currently rate control, with rhythm control being reserved to improve symptoms that persist despite adequate rate control.

Antiarrhythmic drugs for rhythm control

Antiarrhythmic drugs double the likelihood of maintaining sinus rhythm compared with no rhythm-control therapy. AF ablation is more effective than antiarrhythmics in maintaining sinus rhythm, including when used first-line, and is well tolerated. However, ablation should not be considered as a one-off curative treatment for AF.

Upstream therapies (mineralocorticoid receptor antagonists, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and sodium-glucose co-transporter-2 inhibitors) have also demonstrated improved maintenance of sinus rhythm.

Dronedarone is associated with a better safety profile than amiodarone and therefore may be considered as a first-line treatment option for rhythm management in some patients but it is not available in Australia. The ATHENA trial showed that dronedarone reduced the risk of hospitalisation due to unexpected cardiovascular events or death from any cause compared with placebo, but the PALLAS study was stopped prematurely as there was an increased rate of heart failure and cardiovascular death when used in patients with chronic AF, which was also seen in the Andromeda trial using this agent in patients with heart failure with or without AF/flutter.

AF burden may also be reduced by lifestyle interventions such as weight loss, increased exercise, and management of sleep apnoea.

AF ablation for rhythm control

Ablation is an important treatment option for AF. In the CASTLE-AF trial, catheter ablation led to reduced AF burden and improved left ventricular ejection fraction compared with drug therapy in patients with AF and heart failure, with similar outcomes in the CABANA trial in the same population, but there has been much discussion about the validity of the results of this trial.

Clinical benefit of early rhythm management

The EAST-AFNET 4 study in patients with AF diagnosed within 12 months before randomisation, who were at risk of stroke, supports early AF treatment, changing the view on early rhythm control as a general treatment concept. The composite of death from cardiovascular causes, stroke, or hospitalisation with worsening heart failure or acute coronary syndrome, was reduced by 21% in patients who received early rhythm control (consisting typically of antiarrhythmic therapy, or, to a lesser degree, ablation), compared to usual care. Safety was similar between groups. Compared to those assigned to usual care, stroke was reduced by about one-third and mortality was 16% lower in patients who had early rhythm control. The beneficial effect of early rhythm control versus usual care was independent of whether patients were symptomatic or asymptomatic. The use of amiodarone and dronedarone in EAST-AFNET 4 and the availability of AF ablation in patients who failed drug therapy may have contributed to this outcome given that they can be safely used in patients with structural heart disease.

The ATTEST trial showed that early ablation as part of standard care was superior to antiarrhythmic therapy alone in delaying progression from recurrent paroxysmal AF to persistent AF, with the effect seen at 1 year and maintained over 3 years.

Next steps

There is an active search for more effective and safer antiarrhythmic drugs such as small conductance calcium-activated potassium channel inhibitors, TWIK-related acid-sensitive potassium channel (TASK-1) inhibitors, slow sodium channel inhibition and multichannel inhibitors, and alternative ablation approaches such as pulsed field ablation or electroporation.

https://tinyurl.com/yje7nrsv

Regulatory News

TGA - Shortage of iodinated contrast media (contrast) diagnostic agents

The TGA has advised of a global shortage of iodinated contrast media (contrast) diagnostic agents and recommends urgent conservation of stock until the shortage is resolved as current supply is very limited. Supply is expected to resume to normal levels in mid-June 2022. Non-ionic contrast agent is used to enhance imaging in a wide range of diagnostic procedures.

To help reduce the impact of this shortage, the TGA has authorised the supply of an overseas-registered product and is also considering other applications of overseas-registered products for supply.

GE Healthcare, the sponsor of iohexol (Omnipaque) and iodixanol (Visipaque), has notified the TGA of a shortage of both these products due to manufacturing and freight issues caused by the recent COVID-19 lockdown in Shanghai, China.

Health professionals should consider the current shortage of iodinated contrast media diagnostic agents when referring patients for imaging. Consider strategies such as:

- Being judicious in the use of contrast for all modalities that use contrast.
- Using non-contrast CT when acceptable.
- Delaying non-urgent scans.
- Using other modalities such as MRI or nuclear medicine.
- Coordinating between private practices and public hospitals to best serve patients in need of contrast CT scans.

RANZCR have published a statement to support health professionals during this shortage. The statement contains information regarding prioritising patients based on clinical need and strategies to conserve current supplies of contrast and manage patient care.

https://tinyurl.com/33anpx5f

News in Brief

Statin use and clinical outcomes in patients with COVID-19: An updated systematic review and meta-analysis

This systematic review and meta-analysis was undertaken to provide an updated summary and to collate the effect of statin use on clinical outcomes in COVID-19 patients using unadjusted and adjusted risk estimates. A search of PubMed, Scopus and Web of Science databases to December 18, 2020 identified 14 high/moderate quality observational studies (n=19,988) reporting clinical outcomes in COVID-19 patients using statins versus those not using statins. While an unadjusted pooled analysis did not show an association between statin use and improved clinical outcomes (OR 1.02; 95% CI 0.69-1.50; P=0.94; I^2 = 94%, random-effects model), an adjusted pooled analysis did show such an association, with statin use significantly reducing the risk of adverse outcomes (OR 0.51; 95% CI 0.41-0.63, P<0.0005; I^2=0%, fixed-effects model).

https://tinyurl.com/3vby6ru5

Risk of bleeding with ticagrelor in elderly patients over 75 years old

A systematic search of seven databases up to May 20, 2020 identified eight eligible studies (five observational studies and three RCTs) examining the risk of bleeding among elderly patients (≥75 years; mean age 77.8 years; n=7032) with acute coronary syndrome receiving ticagrelor versus clopidogrel. During a mean follow-up of 12 months, there was a 20% higher risk of a bleeding event with ticagrelor versus clopidogrel (pooled RR 1.20; 95% CI 1.03-1.40; P=0.017); however, there was no significant difference in risk of major bleeding (pooled RR 1.32; 95% CI 0.91-1.92; P=0.15) or minor bleeding (pooled RR 1.09; 95% CI 0.76-1.58; P=0.64).

https://tinyurl.com/4nvuxewb

COVID-19 Resources for Cardiologists

CSANZ https://tinyurl.com/y3xp2729
ACC https://tinyurl.com/y68aud3a
ESC https://tinyurl.com/wn3fsts

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ACRA https://tinyurl.com/y4yj8xb5
CSANZ https://tinyurl.com/3mwt5ttr
Cardiac Skills Australia https://tinyurl.com/zkzlelb
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with Professor Peter Macdonald and Dr John Atherton
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Interventional Cardiology Research Review
with Conjoint Professor Craig Juergens
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Product Review – Inclisiran for reduction of low-density lipoprotein cholesterol
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American College of Cardiology 2022 Conference Review
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