



Review

Update to Evidence-Based Secondary Prevention Strategies After Acute Coronary Syndrome

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ABSTRACT

A recent acute coronary syndrome provides an opportunity to optimise secondary prevention strategies to reduce the risk of future cardiovascular events. This review provides an updated synopsis of current evidence-based approaches. New clinical trial data on the use of antiplatelet and anticoagulants allow choices of the selection and duration of treatment. Lipid lowering after an acute coronary syndrome is now enhanced, with proprotein convertase subtilisin-kexin type 9 inhibitors providing added benefit on top of statin and ezetimibe treatment in high-risk patients. In addition, a recent trial of icosapent ethyl, a highly purified ethyl ester of eicosapentaenoic acid, addresses residual risk in patients with elevated triglycerides already treated with

RÉSUMÉ

La survenue récente d'un syndrome coronarien aigu offre l'occasion d'optimiser les stratégies de prévention secondaire en vue de réduire le risque d'événements cardiovasculaires futurs. Le présent article de synthèse offre une vue d'ensemble actualisée des approches contemporaines fondées sur des données probantes. Les nouvelles données d'essais cliniques sur l'utilisation d'antiplaquetaires et d'anticoagulants permettent de choisir un traitement et sa durée. La réduction des lipides après la survenue d'un syndrome coronarien aigu se trouve maintenant améliorée, les bienfaits des inhibiteurs de la proprotéine convertase subtilisine/kexine de type 9 s'ajoutant à ceux du traitement par des statines et l'ézétimibe chez les patients à haut

In 2016, our review of strategies for evidence-based secondary prevention of cardiovascular events after acute coronary syndrome (ACS) was published.¹ We now update these approaches based on information that has since become available. This update has a similar approach to the original review and is not intended to be a new clinical practice guideline or designed to be a systematic review. The goal is to provide a platform for discussion about the role of new treatments in secondary prevention after an ACS.

Most of the secondary prevention strategies in the original algorithm are unchanged. However, new data support the use of (1) oral antithrombotic therapy in addition to, or instead of, acetylsalicylic acid (ASA) in high-risk patients after ACS; (2) proprotein convertase subtilisin-kexin type 9 (PCSK9) inhibitors; (3) icosapent ethyl (EPA); and (4) glucose-lowering agents with cardiovascular benefit in patients with type 2 diabetes mellitus.

Figure 1 shows the original strategies described in 2016 for secondary prevention and highlights the updated/new features in bold type. The algorithm continues to stress the need for lifestyle and cardiovascular disease (CVD) risk factor management, including referral to a cardiac rehabilitation program.

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Ethics Statement: This is a review and all the studies and all the studies quoted has adhered to relevant ethical guidelines.

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See page 412 for disclosure information.

Oral Antithrombotic Therapy in Addition to or Instead of ASA

Dual oral antiplatelet therapy during and after ACS was established after the Clopidogrel in Unstable Angina to

statins. The use of both sodium-glucose co-transporter 2 inhibitors and glucagon-like peptide-1 receptor agonists in patients with type 2 diabetes reduces cardiovascular events independently of glucose lowering.

Prevent Recurrent Ischemic Events (CURE) trial² with the superiority of ASA and clopidogrel compared with ASA alone. Subsequently, both ticagrelor³ and prasugrel⁴ were shown to be superior to clopidogrel. The open label Intracoronary Stenting and Antithrombotic Regimen: Rapid Early Action for Coronary Treatment 5 (ISAR REACT 5) study showed potential outcome advantages for prasugrel compared with ticagrelor. However, because prasugrel will not be available in the near future, the standard of care for dual antiplatelet therapy (DAPT) after ACS has become ASA plus ticagrelor for 1 year. Furthermore, the increased bleeding rates associated with DAPT have led to a search for alternative strategies (Table 1).

A number of recent trials have assessed the potential for shorter duration (eg, 1 or 6 months vs 12 months) of DAPT, including in patients with ACS.^{5,6} However, these open-label, noninferiority design trials, although showing reduced risk of bleeding with shorter vs 1-year duration of DAPT (most commonly using clopidogrel), have also demonstrated numeric (or statistically significant) increases in ischemic events, including reinfarction and stent thrombosis. Thus, unless the patient is at particularly high risk for bleeding, ticagrelor or prasugrel (in preference to clopidogrel) should be used for at least 1 year after ACS/percutaneous coronary intervention (PCI), as per the Canadian Cardiovascular Society Antiplatelet Guideline recommendations.⁷

The Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy vs a Current-Day Intensive Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and Biomatrix Family Drug-Eluting Stents (GLOBAL LEADERS),⁸ Smart Angioplasty Research Team: Comparison Between P2Y₁₂ Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents (SMART-CHOICE),⁹ and Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention (TWILIGHT)¹⁰ trials have examined the potential for reducing bleeding by using P2Y₁₂ receptor inhibitor monotherapy vs DAPT after PCI, including in patients after ACS.^{8,10,11} These studies show that after an initial period of DAPT, patients post-PCI, including those with ACS, could be considered for P2Y₁₂ inhibitor monotherapy, particularly in patients at high bleeding risk. However, not all of these trials were adequately powered to assess ischemic outcomes post-ACS.

Since the 2016 recommendation for consideration of extension of DAPT with a P2Y₁₂ receptor inhibitor and ASA in those patients vascular disease who tolerated (without significant bleeding) these and were adherent to DAPT from the index ACS to approximately 1 year, additional clinical trials such as Prevention of Cardiovascular

risque. En outre, un essai récent portant sur l'icosapent éthylique hautement purifié de l'acide eicosapentaénoïque, aborde le risque résiduel chez les patients présentant une hypertriglycéridémie déjà traités par des statines. L'utilisation d'inhibiteurs du cotransporteur sodium-glucose de type 2 et d'agonistes des récepteurs du peptide-1 apparenté au glucagon chez les patients atteints de diabète de type 2 limite les événements cardiovasculaires indépendamment de la diminution de la glycémie.

Events in Patients With Prior Heart Attack Using Ticagrelor Tablets Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54)¹² trial give continued support for this approach. Subgroup analyses from the PEGASUS-TIMI 54 trial¹³ have identified particularly high-risk patients after MI who derive large absolute benefit of ticagrelor 60 mg twice daily added to ASA vs ASA alone. Those with diabetes, chronic kidney disease (ie, estimated glomerular filtration rate [eGFR] < 60 mL/min/1.73 m²),¹⁴ peripheral artery disease (PAD),¹⁵ and multivessel coronary artery disease (CAD),¹⁶ all derived important outcome benefits with ticagrelor compared with placebo. In most subgroups, the incremental major bleeding risk observed with ticagrelor was similar in relative terms to that seen in the overall trial population when compared with ASA alone.

A prospective economic substudy of the PEGASUS-TIMI 54 trial (assessed from a US healthcare system perspective with typically higher drug and hospitalization costs) identified several high-risk subgroups, including patients with > 1 prior MI, multivessel disease, diabetes, and renal dysfunction, and particularly those aged < 75 years and those with PAD, in whom the incremental cost-effectiveness ratio was comparable to several other secondary prevention approaches currently used in clinical practice.¹⁷ Despite this evidence for cost-effectiveness, there is a lack of Canadian provincial formulary approval of extended ticagrelor use (beyond the first year).

Oral Anticoagulation Therapy

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial randomly assigned 27,395 participants with chronic atherosclerotic cardiovascular disease (ASCVD) (CAD or PAD, including those with carotid artery disease) to receive rivaroxaban (2.5 mg twice daily) plus ASA (100 mg once daily), rivaroxaban (5 mg twice daily), or ASA (100 mg once daily) in a double-blind fashion.¹⁸ Details of the study are shown in Table 2.

The primary outcome of a composite of cardiovascular (CV) death, stroke, or MI (mean follow-up 23 months) occurred in significantly fewer patients in the rivaroxaban 2.5 mg twice daily plus ASA group than in the ASA alone group (4.1% vs 5.4%; hazard ratio [HR], 0.76; 95% confidence interval [CI], 0.66-0.86; *P* < 0.001).¹⁸ CV death was reduced 22%, as was all-cause mortality 18% and stroke 42%.¹⁹ Although major bleeding events (~50% of which were gastrointestinal) occurred in more patients in the rivaroxaban plus ASA group (3.1% vs 1.9%; HR, 1.70 [1.40-2.05]; *P* < 0.001), there was no significant difference in intracranial or

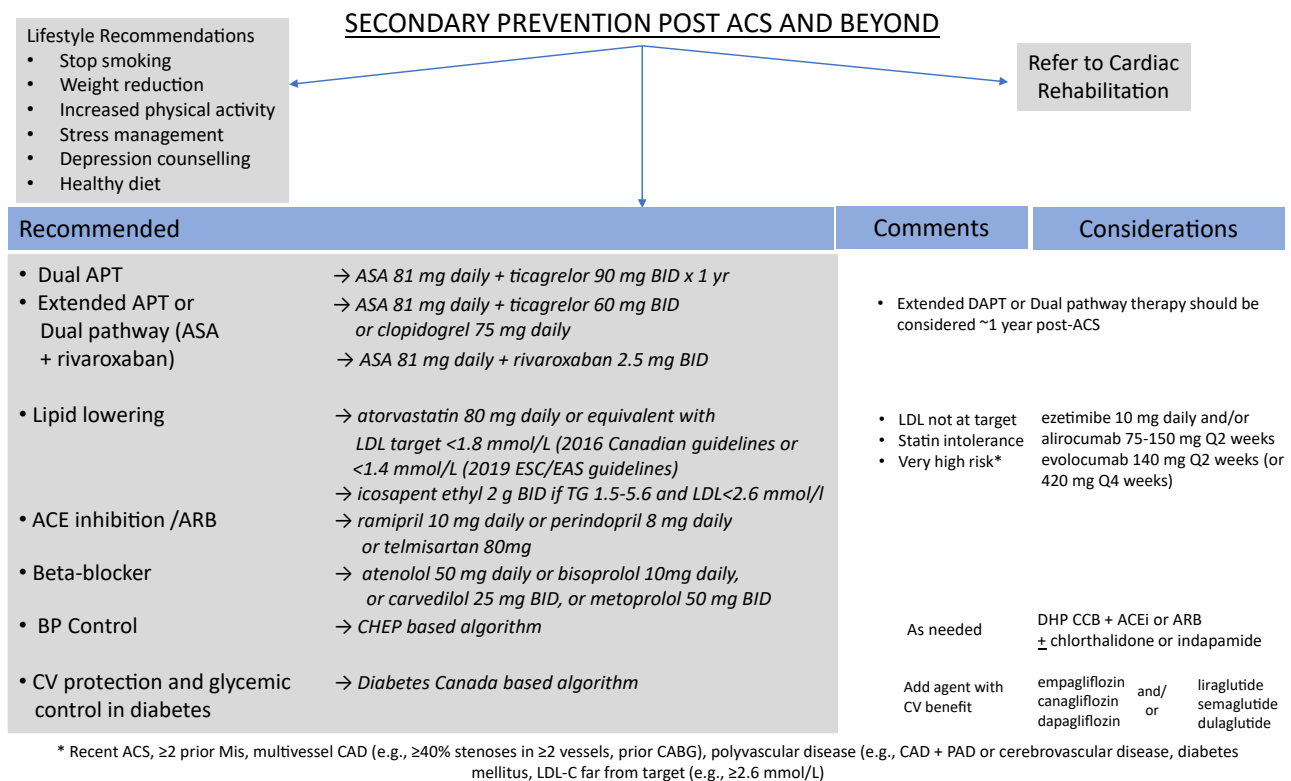


Figure 1. Algorithm for the secondary prevention of cardiovascular events in patients with recent acute coronary syndrome (ACS). ACE, angiotensin-converting enzyme; ACEi, angiotensin-converting enzyme inhibitor; APT, antiplatelet therapy; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; BID, twice per day; BP, blood pressure; CABG, coronary artery bypass grafting; CAD, coronary artery disease; CHEP, Canadian Hypertension Education Program; CV, cardiovascular; DAPT, dual antiplatelet therapy; DHP CCD, dihydropyridine calcium channel blocker; EAS, European Atherosclerosis Society; ESC, European Society of Cardiology; LDL, low-density lipoprotein; PAD, peripheral artery disease; TG, triglyceride.

fatal bleeding between these 2 groups. Further, the net clinical benefit over time (eg, absolute risk differences for major adverse cardiovascular events compared with fatal bleeding or symptomatic bleeding into a critical organ) was highlighted in a recent COMPASS analysis that concluded that most excess bleeding occurred during the first year after randomization, was of mild or moderate intensity, and was managed with conventional supportive therapy.²⁰ In contrast, there was no primary outcome benefit in the rivaroxaban-alone compared with the ASA-alone group, and major bleeding events occurred more frequently in the rivaroxaban-alone group.

Major adverse limb events (severe limb ischemia leading to an intervention [angioplasty, bypass surgery, amputation, thrombolysis] or major amputation above forefoot due to vascular cause) also occurred significantly less frequently in those receiving rivaroxaban plus ASA compared with ASA-alone (1% vs 2%; HR, 0.54 [0.35-0.82]; $P = 0.004$), including those with CAD and symptomatic or asymptomatic (ankle-brachial index < 0.9) PAD.^{21,22}

Subgroup analyses demonstrated consistency of benefit for the primary and key secondary end points, including for all-cause death, including among those with CAD,^{18,23} with or without PAD,^{18,21} recent CABG (although no differences in graft patency were observed),²⁴ diabetes,¹⁸ and CKD.^{18,25} Although the majority of patients with prior MI in COMPASS were > 2 years removed from their most recent event,

there was also consistency of benefit among those ($n = 2423$) whose MI occurred within the previous 2 years.²³ Given the higher-risk nature of several of these subgroups, consistent relative reduction in events with rivaroxaban plus ASA compared with ASA alone translates into greater absolute risk reductions.

The findings from COMPASS are remarkably consistent with those observed in the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome 2-Thrombolysis in Myocardial Infarction 51 (ATLAS ACS-2-TIMI 51) trial.²⁶ ATLAS ACS 2-TIMI 51 tested rivaroxaban (2.5 mg twice daily or 5 mg twice daily) in addition to ASA or DAPT in patients with recent ACS and demonstrated that rivaroxaban resulted in a lower rate of CV death, MI, or stroke than placebo, and the dose of 2.5 mg twice daily significantly lowered CV death and all-cause mortality. Rivaroxaban, even the 2.5 mg twice daily arm, resulted in a significant increase in major bleeding (2.1% vs 0.6%, $P < 0.001$) and intracranial haemorrhage (0.6% vs 0.2%, $P = 0.009$), without a significant increase in fatal bleeding. The mean duration of rivaroxaban treatment in ATLAS ACS 2-TIMI 51 trial was approximately 13 months; in contrast, patients with prior MI in COMPASS were enrolled a mean of approximately 7 years after the acute event and continued to receive treatment for a mean of 23 months.

Table 1. Antiplatelet therapy

Strategy	Patients	Treatment	Outcome
DAPT after ACS CURE ²	Acute non–ST-elevation ACS N = 12,562	Clopidogrel 300 mg then 75 mg daily + ASA vs ASA	Clopidogrel + ASA reduced CVD/MI/stroke 20% Major bleeding increased 38% but no increase in life-threatening or fatal bleeding
PLATO ³	Acute ACS with or without ST-elevation ACS N = 18,624	Ticagrelor 180 mg then 90 mg daily vs clopidogrel 300 mg then 75 mg daily for 12 mo All patients taking ASA	CVD/MI/stroke reduced 16%; HR, 0.84 (0.77-0.92) MI, CV 5/8/20 and all-cause death significantly reduced Increased non-CABG–related bleeding
TRITON–TIMI 38 ⁴	Acute ACS scheduled for PCI N = 13,608	Prasugrel 60 mg then 10 mg daily vs clopidogrel 300 mg then 75 mg daily All patients taking ASA	CVD/MI/stroke reduced 19%; HR, 0.81 (0.73-0.90) Reduced MI, stent thrombosis, urgent revascularization Major bleeding increased 32%, increased life-threatening and fatal bleeding
Shorter duration of DAPT Multiple open-label noninferiority trials ^{5,6}		Duration of DAPT 1, 6 mo vs 1 y	Nonstatistical increase in ischemic events
Mono APT vs DAPT GLOBAL LEADERS ⁸		ASA + ticagrelor for 1 mo then ticagrelor for 23 mo vs ASA + clopidogrel for 12 mo then ASA for 12 mo	At 2 y ticagrelor: NS lower death/MI; HR, 0.87 (0.75-1.01) Bleeding rates in patients with ACS lower with 1 mo DAPT/23 mo ticagrelor
SMART-CHOICE ⁹	Post PCI (58% post-ACS) N = 2993	3 mo DAPT followed by DAPT vs monotherapy with P2Y ₁₂	Similar all-cause death/MI/stroke. Only 5 stent thromboses. Bleeding lower in monotherapy 2.0% vs 3.4%)
TWILIGHT ¹⁰	Post-PCI (30% post-ACS) with 1 high ischemic or bleeding risk N = 7119	3 mo DAPT without bleeding or ischemic event, then ticagrelor + ASA vs ticagrelor	Bleeding (BARC type 2, 3, or 5) 4.0% vs 7.1%; HR, 0.56 (0.45-0.68) No difference in all-cause mortality/MI/stroke Similar outcomes in patients with an without ACS
Extension of DAPT treatment period with P2Y₁₂i PEGASUS/TIMI 54 ¹²	Prior MI 1-3 y earlier, N = 21,162	ASA + ticagrelor 90 mg BID vs ticagrelor 60 mg BID vs placebo	2 doses of ticagrelor reduced CVD/MI/stroke by similar amounts compared with placebo (90 mg 15%, 60 mg 16%) TIMI major bleeding increased (90 mg 2.6%, 60 mg 2.3% placebo 1.06%) Similar ICH/fatal bleeding

ACS, acute coronary syndrome; APT, antiplatelet therapy; ASA, acetylsalicylic acid; BARC, Bleeding Academic Research Consortium; BID, twice per day; CABG, coronary artery bypass grafting; CV, cardiovascular; CVD, cardiovascular disease; CURE, Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events; DAPT, dual antiplatelet therapy; GLOBAL LEADERS, Ticagrelor Plus Aspirin Followed by Ticagrelor Monotherapy vs a Current-Day Intensive Dual Antiplatelet Therapy in Patients Undergoing Percutaneous Coronary Intervention With Bivalirudin and Biomatrix Family Drug-Eluting Stents; HR, hazard ratio; ICH, intracranial haemorrhage; MI, myocardial infarction; PEGASUS/TIMI 54, Prevention of Cardiovascular Events in Patients With Prior Heart Attack Using Ticagrelor Tablets Compared to Placebo on a Background of Aspirin–Thrombolysis in Myocardial Infarction 54; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; SMART CHOICE, Smart Angioplasty Research Team: Comparison Between P2Y₁₂ Antagonist Monotherapy vs Dual Antiplatelet Therapy in Patients Undergoing Implantation of Coronary Drug-Eluting Stents; TIMI, thrombolysis in myocardial infarction; TRITON–TIMI 38, TRial to assess Improvement in Therapeutic Outcomes by optimizing platelet inhibition with prasugrel–Thrombolysis in Myocardial Infarction 38; TWILIGHT, Ticagrelor With Aspirin or Alone in High-Risk Patients After Coronary Intervention.

Despite the clear benefits in reducing ischemic events with extended DAPT or rivaroxaban plus ASA in patients post-MI, dual inhibition with antiplatelet or anticoagulation is also associated with increased bleeding risk. Thus, the identification of the key risk factors associated with higher ischemic and bleeding risk may help the clinician and patient in the decision-making process. Several risk scores, assessing mainly

bleeding but sometimes incorporating elements of ischemic risk, have been developed.²⁷⁻³⁰ However, these are generally focused on post-PCI (and not exclusively patients post-ACS), have been developed mainly within clinical trial populations, and have not been generally well validated in routine clinical practice.³¹ A recent observational analysis from Sweden included > 100,000 invasively managed patients with MI

Table 2. Oral anticoagulation after ACS

	Patients	Treatment	Outcomes
COMPASS ¹⁸	Chronic ASCVD (CAD (91%) or PVD (both cerebrovascular and lower limb vascular disease) For patients aged < 65 y, also ASCVD in 2 territories or 2 additional risk factors (current smoker, diabetes, CKD, or nonlacunar stroke) 62% with prior MI (mean time 7 y) Excluded patients needing DAPT or OAC Stroke < 1 mo, HF, LVEF < 30%, eGFR < 15 mL/min/1.73 m ² N = 27,395	Rivaroxaban 2.5 mg BID +ASA vs rivaroxaban 5 mg BID vs ASA	Study stopped prematurely because of early benefit of rivaroxaban For rivaroxaban 2.5 mg BID +ASA CVD/MI/stroke reduced 24% (HR, 0.76; 0.66-0.86) CVD reduced 22% (HR, 0.78; 0.64-0.96) All-cause mortality reduced 18% MI not significantly reduced No additional benefit from rivaroxaban 5 mg BID Major limb adverse events (severe limb ischemia leading to amputation or revascularisation) reduced (HR, 0.54; 0.34-0.82) Major bleeding increased 3.9% vs 1.9% (50% was GI) HR, 1.7 (1.40-2.05) No increase in intracranial or fatal bleeding
ATLAS ACS-2 TIMI 51 ²⁶	Recent ACS	On ASA or DAPT Rivaroxaban 2.5 mg BID or 5 mg BID vs placebo for 13 mo	Rivaroxaban reduced primary EP (CVD/MI/stroke) 16%; HR, 0.84 (0.74-0.96). Similar primary EP benefits with 2.5 mg BID and 5 mg BID Rivaroxaban 2.5 mg BID reduced CVD (2.7% vs 4.5%) but no reduction of CVD with 5 mg BID Rivaroxaban 2.5 mg BID: major bleeding increased 2.1% vs 0.2%, intracranial haemorrhage 0.6% vs 0.2%, but no increase in fatal bleeding

ACS, acute coronary syndrome; APT, antiplatelet therapy; ASA, acetylsalicylic acid; ASCVD, atherosclerotic cardiovascular disease; ATLAS ACS-2 TIMI 51, the Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects With Acute Coronary Syndrome 2-Thrombolysis in Myocardial Infarction 51; BID, twice per day; CAD, cardiovascular artery disease; CKD, chronic kidney disease; COMPASS, Cardiovascular Outcomes for People Using Anticoagulation Strategies; CVD, cardiovascular disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; EP, end point; GI, gastrointestinal; HF, heart failure; HR, hazard ratio; ICH, intracranial haemorrhage; LVEF, left ventricular ejection fraction; MI, myocardial infarction; OAC, oral anticoagulant; PAD, peripheral artery disease; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction.

(2006-2014), of whom 21% experienced CV death, MI, or stroke and 6% major bleeding during a median of 3.6 years of follow-up.³² Six factors (age \geq 65 years, CKD, diabetes, multivessel disease, prior bleeding, and prior MI) were identified as being independently associated with ischemic events, and all but prior MI were also independently associated with major bleeding. The majority (54%) had \geq 2 risk factors, and with each added risk factor, there was a marked but gradual increase in the incidence of ischemic events; this was also seen for major bleeding, but to a lesser extent and largely driven by prior bleeding as the strongest risk factor.

These findings suggest that for the majority of patients with prior MI who would have been eligible for the PEGASUS-TIMI 54 or COMPASS trial, particularly those without prior major bleeding, the high ischemic risk (including CV and all-cause mortality) warrants consideration of extended DAPT (eg, ticagrelor 60 mg twice daily plus ASA) or dual pathway (rivaroxaban 2.5 mg twice daily plus ASA) as effective secondary prevention therapy. Some provincial formularies provide coverage for the use of ticagrelor 90 mg but not 60 mg twice daily; thus, the 60 mg twice daily dosing in the PEGASUS-TIMI 54 trial demonstrated similar cardiovascular efficacy benefit but

with a trend toward less excess bleeding than the 90 mg twice daily.^{15,33} Clopidogrel could be considered an alternative, particularly when access to ticagrelor or rivaroxaban is not possible, given the benefits observed in a subgroup (previous MI) analysis of the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilisation Management and Avoidance (CHARISMA) trial, although the overall trial primary outcome was neutral when compared with ASA alone.

Lipid Modification Therapy

Clinical trials discussed in this section are summarised in Table 3. High-intensity statin therapy (ie, atorvastatin 40-80 mg/day or rosuvastatin 20-40 mg/day) remains the cornerstone of lipid-lowering treatment in patients post-ACS.^{34,35} On the basis of the Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) trial,³⁶ for those with a recent ACS, the 2016 Canadian Dyslipidemia Guidelines suggested consideration be given to more aggressive targets, including a low-density lipoprotein cholesterol (LDL-C) < 1.8 mmol/L, noting that "this might require the combination of ezetimibe (or other nonstatin medications) with maximally tolerated statin."³⁴

Table 3. Lipid modification therapy

	Patients	Strategy	Outcome	Comments
High-intensity statins PROVE IT 22 ³⁵	4162 patients with ACS in previous 10 d	Pravastatin 40 mg vs atorvastatin 80 mg	LDL-C Pravastatin 2.46 mmol/L Atorvastatin 1.60 mmol/L At 24 mo primary EP (all-cause death, MI, stroke, unstable angina, coronary revascularization) reduced 16% (HR, 0.84-0.95)	
Addition of ezetimibe IMPROVE IT ³⁶	18,144 patients with ACS in previous 10 d, and LDL-C 1.3-2.6 mmol/L	Ezetimibe + simvastatin vs simvastatin	LDL-C Simvastatin 1.8 mmol/L Simvastatin + ezetimibe 1.4 mmol/L. At 6 y primary EP (CVD, MI, stroke, unstable angina, coronary revascularization) reduced (HR, 0.94; 0.89-0.99). Absolute risk reduction 2%	Increased benefit in patients with diabetes
Addition of PCSK9 FOURIER ³⁷	Established ASCVD 81% with prior MI LDL C > 1.8 mmol/L	Maximally tolerated statin + evolucumab vs placebo	LDL-C reduced 59% to 0.78 mmol/L At 2.2 y primary EP (CVD, MI, stroke, unstable angina, coronary revascularization) reduced (HR, 0.85 (0.79-0.92) CVD/MI/stroke reduced (HR, 0.80 (0.73-0.88) Lower event rates relate to achieved LDL-C even to < 0.2 mmol/L	Increased minor injection site reaction Greater benefit with • ≥ 2 prior mo • MI < 2 y • Extensive CAD
ODYSSEY OUTCOMES ³⁸	18,924 patients with prior ACS 1-12 mo, and LDL ≥ 1.8	Maximally tolerated statin + alirocumab vs placebo adjusted to achieve LDL-C 0.65-1.29 mmol/L	LDL-C reduced 63% to 0.98 mmol/L At 2.8 y primary EP (CVD, MI, stroke, unstable angina, coronary revascularization) reduced 15%; HR, 0.85 (0.78-0.93) Nonfatal MI and stroke significantly reduced	Increased minor injection site reaction
REDUCE-IT ⁵¹	8179 patients with established CVD (71%) or ≥ 50 y with DM and CV risk factor (29%) with fasting triglycerides 1.52-5.63 mmol/L and LDL-C 1.06-2.59 mmol/L on a stable dose of a statin for ≥ 4 wk	Icosapent ethyl 2 g twice daily vs placebo added to maximally tolerated statin therapy	Primary EP (CVD, MI, stroke, revascularization, unstable angina) HR, 0.75 (0.68-0.83) Secondary EP (CVD, MI, stroke) HR, 0.74 (0.65-0.83) CV death HR, 0.80 (0.66-0.98)	Small increase in hospitalization for atrial fibrillation (3.1% vs 2.1% <i>P</i> = 0.004) and serious bleeding (2.7 vs 2.1% <i>P</i> = 0.06)

ACS, acute coronary syndrome; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; CV, cardiovascular; CVD, cardiovascular disease; EP, end point; HR, hazard ratio; IMPROVE-IT, Improved Reduction of Outcomes: Vytorin Efficacy International Trial; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; ODYSSEY OUTCOMES, Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab; PROVE IT 22, Pravastatin or Atorvastatin Evaluation and Infection Therapy—Thrombolysis in Myocardial Infarction 22; REDUCE-IT, Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial.

Table 4. Glucose-lowering agents with CV benefits

	Patients	Treatment	Outcomes
SGLT2 inhibitors			
EMPA-REG Outcome ⁵⁶	T2DM A ₁ C 7.0%-10.0% Established CVD eGFR > 30 mL/min/1.73 m ² N = 7020	Empagliflozin 10 mg vs 5 mg vs placebo Observation time 3.2 y	CVD/MI/stroke; HR, 0.86 (0.74-0.99) CVD reduced 38% All-cause mortality reduced 32% HFH reduced 35%
CANVAS ⁵⁷	T2DM A ₁ C 7.0%-10.5% Established CVD (72%) or multiple ASCVD risk factors eGFR > 30 mL/min/1.73 m ² Follow-up 3.6 y N = 10142	Canagliflozin	MACE reduced 14%; HR, 0.86 (0.75-0.97) HFH reduced 33%; HR, 0.67 (0.52-0.87) 2-fold increase in peripheral lower limb amputations
DECLARE-TIMI 58 ⁵⁸	T2DM A ₁ C 6.5%-12% Established CVD or multiple ASCVD risk factors (10,160) eGFR > 30 mL/min/1.73 m ² Follow-up 4.2 y N = 17160	Dapagliflozin 10 mg vs placebo	CVD/HFH reduced 17% (HR, 0.73-0.95) MACE not reduced CVD not reduced HFH reduced; HR, 0.73 (0.61-0.88) Genital infection increased Diabetic ketoacidosis increased 0.3% vs 0.1%
CREDESCENCE ⁵⁹	T2DM A1C Albuminuria CKD eGFR 30-90 + albuminuria ACR 3000-5000 mg/g Follow-up 2.62 y N = 4401	Canagliflozin 100 mg vs placebo	ESKD/doubling creatinine/renal or cardiac death reduced 30%; HR, 0.70 (0.70-0.82) CVD reduced 20% HFH reduced 29% No increase amputations of fractures
<i>GLP-1 RA</i> LEADER ⁶²	T2DM + established CVD or risk factors Follow-up 3.8 y N = 9340	Liraglutide s/c daily vs placebo	CVD/MI/stroke reduced 13%; HR, 0.87 (0.78-0.97) CVD reduced 22%, no reduction HFH Increase GI adverse effects
SUSTAIN 6 ⁶³	T2DM + established CVD (83% with CVD or CKD) or risk factors	Semaglutide 0.5-1.0 mg s/c weekly	CVD/MI/stroke reduced 26%; HR, 0.74 (0.58-0.95) Nonfatal stroke reduced 39%
REWIND ⁶⁴	T2DM + established CVD (83% with CVD or CKD) or risk factors FU 5.4 y	Dulaglutide 1.5 mg s/c weekly vs placebo	CVD/MI/stroke reduced 12%; HR, 0.88 (0.79-0.99) Increased GI adverse effects
Harmony outcomes ⁶⁵	T2DM and CVD N = 9463	Albiglutide 30-50 mg s/c weekly, FU 1.6 y	CVD/MI/stroke reduced 22%; HR, 0.78 (0.68-0.90)

ACR, albumin to creatinine ratio; ASCVD, atherosclerotic cardiovascular disease; CANVAS, **Canagliflozin Cardiovascular Assessment Study**; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; CREDESCENCE, **Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation**; DECLARE-TIMI 58, **Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58**; eGFR, estimated glomerular filtration rate; EMPA-REG Outcome, **Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients**; ESKD, end-stage kidney disease; FU, follow-up; GI, gastrointestinal; GLP-1 RA, glucagon-like peptide-1 receptor agonist; HARMONY, **albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease**; HFH, heart failure hospitalisation; HR, hazard ratio; LEADER, **Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results**; MACE, major adverse cardiovascular events; MI, myocardial infarction; REWIND, **Researching Cardiovascular Events With a Weekly Incretin in Diabetes**; s/c, subcutaneously; SGLT2, sodium-glucose co-transporter 2; T2DM, type 2 diabetes mellitus.; SUSTAIN 6, **Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes 6**.

Recent data on the PCSK9 inhibitors evolocumab and alirocumab^{37,38} have shown the additive cardiovascular benefit of further LDL reduction in patients with a recent ACS mainly receiving high-intensity statin therapy.

The **Further Cardiovascular Outcomes Research With PCSK9 Inhibition in Subjects With Elevated Risk (FOURIER)** trial³⁷ was a double-blind, placebo-controlled study with the PCSK9 inhibitor evolocumab in patients aged 40 to 85 years with established atherosclerotic CVD (including 81% with a prior myocardial infarction [MI]) and LDL-C \geq 1.8 mmol/L or non-HDL-C \geq 2.6 mmol/L despite maximally tolerated statin therapy. Relevant exclusion criteria were recent MI or stroke within 4 weeks, planned or expected cardiac surgery or revascularization within 3 months after randomization, New York Heart Association class III-IV HF, or left ventricular ejection

fraction < 0.30. After 48 weeks, LDL-C was reduced 59% to 0.78 mmol/L with evolocumab (140 mg every 2 weeks or 420 mg monthly subcutaneously). After a median follow-up of 2.2 (interquartile range, 1.8-2.5) years, the primary end point (time to first CV death, MI, stroke, hospitalization for unstable angina, or coronary revascularization) was reduced by 15% (HR, 0.85; 95% confidence interval [CI], 0.79-0.92) and the secondary end point (CV death, MI, or stroke) by 20% (HR, 0.80; 95% CI, 0.73-0.88). Several additional secondary end points (eg, MI, stroke, coronary revascularization) were also significantly lower, yet no differences were observed between evolocumab and placebo for CV or all-cause mortality. There was no significant difference between the evolocumab and placebo groups with regard to adverse events (including new-onset diabetes and neurocognitive events), with the exception of injection-site reactions, which were

more common with evolocumab (2.1% vs 1.6%). In a pre-specified secondary analysis of 25,982 patients (94%) in FOURIER who had an LDL-C measured at 4 weeks (and who had not experienced a primary end point event), there was a highly significant linear relationship between lower LDL-C concentrations and lower risk of the primary and secondary efficacy composite end points; this extended to the bottom first percentile (LDL-C < 0.2 mmol/L).³⁹ Conversely, no significant association was observed between achieved LDL-C and safety outcomes, either for all serious adverse events or any of the other 9 prespecified safety events.

As part of another prespecified analysis, a total of 22,351 patients (81% of overall trial) had a prior MI and were stratified on the basis of the (1) number of prior MIs (24% had ≥ 2 prior MIs); (2) timing of prior MIs (38% had their qualifying MI within 2 years of randomization; median time from that MI was 0.6 (0.3-1.2) years); and (3) extent of CAD (25% had residual multivessel CAD defined as $\geq 40\%$ stenosis in ≥ 2 large vessels).⁴⁰ The relative risk reductions (18%-21%) with evolocumab for the primary end point tended to be greater in the high-risk subgroups. Given the higher baseline risk, the respective absolute risk reductions at 3 years exceeded 3% in the high-risk groups (3.4%, 3.7%, and 3.6%) vs approximately 1% in the low-risk groups (0.8%, 1.3%, and 1.2%).

The Evaluation of Cardiovascular Outcomes After an Acute Coronary Syndrome During Treatment With Alirocumab (ODYSSEY OUTCOMES) trial³⁸ was a double-blind, placebo-controlled study with the PCSK9 inhibitor alirocumab in 18,924 patients ≥ 40 years of age with an ACS (MI or high-risk unstable angina) 1-12 (median time 2.6 [1.7-4.3]) months before randomization and an LDL-C ≥ 1.8 mmol/L, non-HDL-C ≥ 2.6 mmol/L, or apolipoprotein B ≥ 0.8 g/L and receiving high-intensity (~89% of patients) or maximally tolerated statin therapy. Relevant exclusion criteria were New York Heart Association class III-IV HF or LVEF < 0.25, coronary revascularization within 2 weeks before, or planned after, randomization, or prior haemorrhagic stroke. The dose of alirocumab (75-150 mg every 2 weeks subcutaneously) was blindly adjusted to achieve an on-treatment LDL-C between 0.65 and 1.29 mmol/L while avoiding sustained LDL-C < 0.4 mmol/L. Alirocumab reduced LDL-C after 4 months by 63% to 0.98 mmol/L and at 48 months by 55% to 1.4 mmol/L. After a median follow-up of 2.8 (2.3-3.4) years, the primary end point (time to first coronary heart disease death, nonfatal MI, fatal or nonfatal ischemic stroke, or unstable angina requiring hospitalization) was reduced by 15% (HR, 0.85 [0.78-0.93]). Nonfatal MI, stroke, and unstable angina hospitalization were significantly reduced. Although both coronary heart disease and CV death were not significantly reduced, all-cause mortality was 15% lower (HR, 0.85 [0.73-0.98]) with alirocumab vs placebo. The incidence of adverse events was similar in the 2 groups, with the exception of local injection-site reactions (3.8% in the alirocumab group vs 2.1% in the placebo group).

In summary, both studies show the cardiovascular benefit of lowering LDL-C below currently recommended levels with a PCSK9 inhibitor. Similar relative benefits were observed in a wide range of subgroups regardless of level of baseline LDL-C,^{37,38} and including patients with diabetes,^{41,42} peripheral arterial⁴³ or polyvascular disease,⁴⁴ type of ACS (ST-elevation,

non-ST-elevation MI or unstable angina),³⁸ type of index ACS management (eg, coronary revascularization) or medical management and time from index ACS to^{37,38} randomisation. Thus, as per the European Society of Cardiology/European Atherosclerosis Society guidelines,⁴⁵ very high-risk patients—including post-ACS—who do not achieve an LDL-C of ≤ 1.4 mmol/L after 4 to 6 weeks despite maximally tolerated statin and ezetimibe, adding a PCSK9 inhibitor is recommended. The greatest absolute risk reductions (with reasonable numbers needed to treat and associated cost-effectiveness) will be realized in those with a recent ACS, residual multivessel CAD (including those with prior CABG,⁴⁶ polyvascular disease (eg, CAD and PAD or cerebrovascular disease), diabetes, and those whose LDL-C remains far from target (eg, ≥ 2.6 mmol/L). Finally, the PCSK9 inhibitors are remarkably safe and well tolerated (ie, indistinguishable adverse event profile compared with placebo apart from a small absolute increase in the frequency of local injection site reactions [erythema, pruritus, bruising]). Further, the lowest levels of LDL-C achieved are associated with the lowest CV event rates and no apparent safety signal, at least over the 2- to 5-year duration of treatment experience in the FOURIER and ODYSSEY OUTCOMES trials.

Elevated triglycerides are an independent marker for an increased risk of ischemic events.⁴⁷ In previous randomized trials, extended-release niacin, fibrates, and n-3 fatty acid supplementation, despite lowering triglyceride levels, have not reduced CV event rates when added to statin therapy.^{48,49} In contrast, in the Japan EPA Lipid Intervention Study (JELIS), 18,645 patients with hypercholesterolemia were randomly assigned to receive low-intensity statin therapy plus 1.8 g of EPA daily or statin therapy alone, and the risk of major coronary events was significantly lower in the EPA plus statin therapy compared with the statin alone group.⁵⁰ However, JELIS was an open-label design study without a placebo group, used a low-intensity statin, and was conducted in a single country. The **Reduction of Cardiovascular Events with Icosapent Ethyl-Intervention Trial (REDUCE-IT)** was an international, multicenter, randomized, double-blind, placebo-controlled study of patients aged ≥ 45 years with established cardiovascular disease or age ≥ 50 years with diabetes mellitus and 1 additional risk factor, who had been receiving statin therapy and who had a fasting triglyceride level of 1.52 to 5.63 mmol/L and a LDL-C level of 1.06 to 2.59 mmol/L. Patients enrolled in the trial included those with prior MI (47%), symptomatic PAD (9%), prior ischemic stroke (6%), or transient ischemic attack (5%).⁵¹ Additional baseline risk factors included hypertension (87%), diabetes mellitus (59%), eGFR < 60 mL/min/1.73 m² (22%), heart failure (18%), and current daily cigarette smoking (15%). Most patients at baseline were taking evidence-based CV medications, including antiplatelet agents (79%), beta-blockers (71%), and an angiotensin-converting enzyme inhibitor or angiotensin receptor blockers (ARBs) (78%). The median LDL-C was 1.94 mmol/L, and fasting serum triglycerides were 2.44 mmol/L (all patients were receiving statin therapy, including high-intensity in 31% and 6% were on ezetimibe at baseline). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. At a median follow-up of 4.9 years, the primary end point composite of CV death, nonfatal MI, nonfatal

stroke, coronary revascularization, or unstable angina, occurred in 17.2% of the patients in the icosapent ethyl group compared with 22.0% of the patients in the placebo group (HR, 0.75 [0.68 to 0.83]; $P < 0.001$). This large absolute difference (4.8%) leads to an overall number-needed-to-treat (over ~ 5 years) of 21. The corresponding key secondary end point (composite of CV death, nonfatal MI, or nonfatal stroke) rates were 11.2% vs 14.8% (HR, 0.74 [0.65-0.83]; $P < 0.001$). Further, the rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including CV death (4.3% vs 5.2%; HR, 0.80 [0.66-0.98]; $P = 0.03$) and fatal or nonfatal stroke (HR, 0.72 [0.55-0.93]). The rate of death from any cause was 6.7% in the icosapent ethyl group vs 7.6% in the placebo group (HR, 0.87 [0.74-1.02]).

The significantly lower risk of major adverse cardiovascular events with icosapent ethyl occurred irrespective of the attained triglyceride level at 1 year (≥ 1.69 or < 1.69 mmol/L), suggesting that the CV risk reduction was not associated with attainment of a more normal triglyceride level.

The overall rates of adverse and serious adverse events leading to study drug discontinuation were similar in the 2 groups. The rate of atrial fibrillation was significantly higher in the icosapent ethyl group (5.3% vs 3.9%), including the prespecified and adjudicated tertiary end point of hospitalization for atrial fibrillation or (3.1% vs 2.1%, $P = 0.004$). The rates of peripheral edema (6.5% vs 5.0%) and serious adverse bleeding (2.7% vs 2.1%; although not for serious intracranial or gastrointestinal bleeding, haemorrhagic stroke end points, or bleeding-associated deaths) were higher with icosapent ethyl; in contrast, the rate of anemia was significantly lower in the icosapent ethyl group (4.7% vs 5.8%), as were the rates of diarrhea (9.0% vs 11.1%) and gastrointestinal adverse events (33.0% vs 35.1%). In prespecified analyses examining not only first events but also recurrent and total ischemic events, an approximate 30% reduction was observed, which will favourably affect evaluations of cost-effectiveness.^{52,53} Health Canada has approved icosapent ethyl based upon REDUCE-IT. A recent analysis of the Ontario population suggests that approximately 25% of patients with ASCVD have hypertriglyceridaemia and “controlled” LDL-C; these patients were demographically similar to those in REDUCE-IT with comparable event rates.⁴⁷ Thus, in patients post-ACS with elevated triglyceride levels despite LDL-C lowering therapy (eg, ≥ 2 mmol/L, recognizing that 10% of the REDUCE-IT population with a baseline triglyceride < 1.69 mmol/L derived similar relative benefit), consideration of icosapent ethyl 2 g twice daily to reduce important CV events is warranted.

Glucose-Lowering Agents With Cardiovascular Benefit

Recent clinical trials have shown that both sodium-glucose co-transporter 2 (SGLT2) Inhibitors and glucagon-like peptide-1 receptor agonist (GLP-1 RA) can reduce CV events in patients with type 2 diabetes mellitus and atherosclerotic CV disease^{54,55} (Table 4). Four cardiovascular outcome trials with SGLT2 inhibitors have been reported, with empagliflozin (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients [EMPA-REG Outcome]⁵⁶),

canagliflozin (Canagliflozin Cardiovascular Assessment Study [CANVAS]⁵⁷), and dapagliflozin (Dapagliflozin Effect on Cardiovascular Events—Thrombolysis in Myocardial Infarction 58 [DECLARE-TIMI 58]⁵⁸) and 1 primary renal outcome (Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation [CREDENCE]⁵⁹) trial. The inclusion criteria for established CVD and renal function differed between these studies: EMPA-REG Outcome included only patients with established CVD, whereas the proportion with CVD was 40% in DECLARE-TIMI 58, 70% in CANVAS, and 50% in CREDENCE. The entry renal function criteria varied from eGFR > 60 mL/min/m² in DECLARE-TIMI 58 to eGFR 30 to 90 mL/min/m² plus urine micro-albumin creatinine ratio > 300 to ≤ 5000 mg/g in CREDENCE. Consequently, the mortality in the populations varied widely from 7.1 CV deaths/1000/year in DECLARE-TIMI 58 to 35/1000/year in CREDENCE.

The major adverse cardiovascular events (MACE) end point was reduced in EMPA-REG Outcome, CANVAS, and CREDENCE, but not reduced in DECLARE-TIMI 58, where the other dual primary end point of CV death/hospitalisation for heart failure was reduced by a significant 17%. Cardiovascular mortality was reduced 38% in EMPA-REG Outcome and 22% in the CREDENCE trial. Hospitalisation for heart failure was reduced 27% to 35%. All 4 trials showed a significant reduction of the composite renal end point, which included progression to macro-albuminuria, doubling or 40% increase of serum creatinine, need for chronic renal replacement therapy, or renal death.

Patients with a baseline history of cardiovascular disease receiving a SGLT2 inhibitor, had a significant reduction of major cardiovascular events, heart failure hospitalisation, and stabilisation of chronic kidney disease. However, in the CANVAS and DECLARE-TIMI 58 studies, patients with multiple risk factors yet no documented CVD, had no reduction of major CV events, yet maintained the heart failure and renal benefits.⁵⁴ However, in the higher-risk patients in the CREDENCE study,⁵⁹ patients with and without a history of CVD had benefit. In the EMPA-REG Outcome trial, patients with a history of MI or stroke had the same CV mortality reduction as those with established ASCVD yet no prior atherothrombotic event.⁶⁰

In the DECLARE-TIMI 58 trial, patients with prior MI had an especially large benefit from dapagliflozin compared with subjects with no history of MI⁶¹ (MACE: prior MI adjusted risk ratio [ARR] 2.6%; HR, 0.84; 95% CI, 0.72-0.99; no prior MI ARR 0% HR, 1.00; 95% CI, 0.81-1.19). Heart failure hospitalisation/CV mortality: prior MI ARR 1.9% HR, 0.81; 95% CI, 0.65-1.00; no prior MI 0.6%; HR, 0.85; 95% CI, 0.72-1.00). Patients with known atherosclerotic CVD but no prior MI had a smaller benefit from dapagliflozin (ARR, 0.2%; HR, 0.98; 95% CI, 0.81-1.19) compared with individuals with a prior MI. There was a greater reduction of MACE in the 2 years after the last acute coronary event with no apparent reduction of MACE if the MI occurred more than 36 months after treatment initiation. Similar reductions of heart failure hospitalisation and of the renal composite endpoint were observed in patients with and without a history of MI. The magnitude of the risk reduction for recurrent CVD events with an SGLT2 inhibitor is similar to that observed with other CV protective treatments such as statins or anti-platelet agents.

The Dapagliflozin (DAPA) Heart Failure study showed that patients with heart failure (with 44% having a history of MI) with or without diabetes had 26% reduced combined CV events (CV death, hospitalisation for HF, or urgent HF visit HR, 0.74; 95% CI, 0.65-0.85). CV death was reduced 18%.

Clinical trials with the 7 GLP-1 RA that are published or top-line results reported show heterogeneity in CV outcomes. Four fully reported studies, **Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results (LEADER)**⁶² with liraglutide, **Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes 6 (SUSTAIN 6)**⁶³ with semaglutide, **Researching Cardiovascular Events With a Weekly Incretin in Diabetes (REWIND)**⁶⁴ with dulaglutide and Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (**Harmony Outcomes**)⁶⁵ with albiglutide show the GLP-1 RA reduced the primary MACE end point. In addition, the results of **Peptide Innovation for Early Diabetes Treatment (PIONEER 6)**⁶⁶ suggests a cardiovascular benefit from oral semaglutide. Yet 2 other trials, the **Evaluation of Lixisenatide in Acute Coronary Syndrome (ELIXA)**⁶⁷ with lixisenatide and the **Exenatide Study of Cardiovascular Event Lowering (EXSCEL)**⁶⁸ with once weekly exenatide, showed no reduction of the primary end points. Liraglutide in the LEADER trial resulted in a 22% reduction of CV mortality, whereas semaglutide in the SUSTAIN 6 trial reduced stroke but not CV mortality. A reduction of heart failure presentation is generally not seen with GLP-1 RA. In patients with and without a history of MI or stroke there was a consistent CV benefit with liraglutide. The impact on coronary and cerebrovascular events and the general lack of impact on heart failure suggest that the CV benefit of GLP-1 RA is likely a vascular protective benefit.

Serious adverse events from both SGLT2 inhibitors⁶⁹ and GLP-1 RA⁷⁰ are infrequent. SGLT2 inhibitors may cause superficial mycotic genital infections, urinary tract infections, diabetic ketoacidosis DKA (may occur with no hyperglycemia), and hypoglycemia (if used in a patient on insulin or a sulfonyleurea). In the EMPA-REG Outcome trial, no increase in serious adverse events were reported. In the CANVAS trials, there was a small increase in adverse events due to volume depletion, yet acute kidney injury was not increased. No increase in volume depletion symptoms was observed in the other 3 trials including the CREDENCE trial with canagliflozin. A small increase in the incidence of diabetic ketoacidosis was observed in DECLARE-TIMI 58 and CREDENCE (2 vs 0.2 events/1000 patients/year). In the CANVAS study, there was a 2-fold increase in amputations: an adverse event that has not been observed in any other SGLT2 inhibitor study including the CREDENCE study. Genital infections with candida species were increased in all the clinical trials, yet they are usually no more than mild to moderate in severity, generally respond rapidly to oral or topical antifungal agents, and rarely result in discontinuation of the SGLT2 inhibitor.

Symptomatic volume depletion and hypotension can be minimised by identification of patients at risk and the adjustment of diuretics and other blood pressure—lowering agents including angiotensin-converting enzyme inhibitor inhibitors and ARBs. Hypoglycemia may be avoided by reducing or discontinuing sulfonyleureas and making small adjustments to

insulin dosage in patients at risk. Mycotic genital infections are probably reduced by good perineal hygiene and patient education. Diabetic ketoacidosis is usually associated with an intercurrent illness and instructing the patient to take a “sick day” temporary discontinuation of the SGLT2 inhibitor during an acute event or need for major surgery will reduce the risk.

The optimal timing to initiate an SGLT2 inhibitor in a patient with a recent ACS is unknown. None of the cardiovascular outcome trials with an SGLT2 inhibitor enrolled patients sooner than 2 months after the acute coronary event. However, the patient with type 2 diabetes and a recent ACS may benefit from early initiation of treatment. For patients who are hemodynamically stable with controlled or no heart failure, and normal blood pressure, it is likely that the benefits of the early initiation of a SGLT2 inhibitor prior to hospital discharge exceed the potential small risks.

GLP-1 RA have no apparent adverse cardiovascular effects. Heart rate is increased approximately 2 to 5 beats/min, and blood pressure reduced. Gastrointestinal adverse effects may limit their use. However, they are usually transient and can be minimised with a slow dose escalation, the consumption of several small meals each day, and avoidance of high fat foods.

Guidelines from Diabetes Canada,⁴² American Diabetes Association,⁷¹ American College of Cardiology,⁷² and the European Association for the Study of Diabetes⁷³ recommend the prescription of a glucose-lowering agent with proven CV benefits in patients with type 2 diabetes and established ASCVD. Guidelines from ADA⁷¹ do not require the patient to have an A1C above the target level and recommend for patients with a risk for heart failure or diabetic kidney disease, an SGLT2 inhibitor is preferable to a GLP1 agonist. Guidelines from the European Society of Cardiology^{74,75} and the Canadian Society of Cardiology⁷⁶ recommend the prescription of an SGLT2 inhibitor to prevent heart failure in patients at risk. Now with the results of the DAPA HF study, dapagliflozin should be considered as part of the treatment of patients with heart failure whether or not they have diabetes.

Although we recognise that there are barriers to care due to differing provincial formulary coverage for SGLT2 inhibitors, GLP1 agonists and PCSK9 inhibitors, we believe that it is our role to promote the use of optimal treatments. However it is important that physicians select the highest risk patients (as discussed earlier) and have initiated maximally tolerated statin therapy and ezetimibe before considering the prescription of an PCSK9 inhibitors.

Colchicine for the Reduction of CV Events

Colchicine, an anti-inflammatory agent principally used in the management of acute gout, has been shown to reduce adverse CV outcomes in patients with a recent MI. The **Colchicine Cardiovascular Outcomes Trial (COLCOT)** trial⁷⁷ enrolled 4745 patients within 30 days of an acute MI and randomised their treatment to colchicine 0.5 mg daily or placebo. After a follow-up of 22 months, the primary composite end point (CV death resuscitated cardiac arrest, MI, stroke, or urgent hospitalization for angina) was reduced 23% by colchicine (HR, 0.77; 0.61-0.96). The rates of CV death and MI were not reduced. Stroke and unstable angina hospitalisation were significantly reduced. Adverse events occurring more frequently in the colchicine treated patients

included diarrhoea (9.7% vs 8.9%) and pneumonia (0.9% vs 0.4%). The trial had some methodological limitations with a high discontinuation rate, and 2.5% of patients lost to follow-up. The primary end point is driven by hospitalisation for angina and revascularisation and not by important end points such as CV death or MI. Consequently, it is not possible to make any recommendations about the use of colchicine for CV protection without more robust data.⁷⁸

Conclusions

Patients with a recent ACS provide an opportunity to initiate and optimise multifaceted strategies to reduce the high risk of recurrent CVD events. Evidence-based recommendations from clinical guidelines support lifestyle modifications (including smoking cessation, weight optimisation, healthy diet, and physical activity) and the use of ASA, statins, angiotensin-converting enzyme inhibitor inhibitors or ARBs, blood pressure control, and glycemic control. These were discussed in the prior publication and are summarised in [Figure 1](#). Extended treatment with antiplatelet agents and the use of anticoagulants provide a strategy to reduce recurrent ACS and CV mortality in patients with increased CV risk yet with a lower threat of bleeding. PCSK9 inhibitors added to statin treatment provides additional reduction of CV event rates and can be considered in patients with very high CV risk or not achieving LDL-C targets despite maximally tolerated statin and ezetimibe treatment. Icosapent ethyl in patients with elevated triglycerides despite LDL-C-lowering therapy leads to significant reductions in CV event rates. Both SGLT2 inhibitors and GLP1-RA reduce CV events (including CV mortality) and should be considered for cardiovascular protection in patients with diabetes and prior MI whatever the A1C.

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