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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Clinical Pathway for Coronary Atherosclerosis in Patients Without Conventional Modifiable Risk Factors

JACC State-of-the-Art Review

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ABSTRACT

Reducing the incidence and prevalence of standard modifiable cardiovascular risk factors (SMuRFs) is critical to tackling the global burden of coronary artery disease (CAD). However, a substantial number of individuals develop coronary atherosclerosis despite no SMuRFs. SMuRFless patients presenting with myocardial infarction have been observed to have an unexpected higher early mortality compared to their counterparts with at least 1 SMuRF. Evidence for optimal management of these patients is lacking. We assembled an international, multidisciplinary team to develop an evidence-based clinical pathway for SMuRFless CAD patients. A modified Delphi method was applied. The resulting pathway confirms underlying atherosclerosis and true SMuRFless status, ensures evidence-based secondary prevention, and considers additional tests and interventions for less typical contributors. This dedicated pathway for a previously overlooked CAD population, with an accompanying registry, aims to improve outcomes through enhanced adherence to evidence-based secondary prevention and additional diagnosis of modifiable risk factors observed. (J Am Coll Cardiol 2023;82:1343–1359) © 2023 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

α-gal = α-galactose-1,3-galactose

ACS = acute coronary syndrome

BMI = body mass index

BP = blood pressure

CAD = coronary artery disease

CHIP = clonal hematopoiesis of indeterminate potential

CRE = Centre for Research Excellence

CVD = cardiovascular disease

ESS = Epworth Sleepiness Scale

HDL-C = high-density lipoprotein cholesterol

Ig = immunoglobulin

LDL-C = low-density lipoprotein cholesterol

MACE = major adverse cardiovascular events

MI = myocardial infarction

OSA = obstructive sleep apnea

PAI = plasminogen activator inhibitor

PRS = polygenic risk score

SMuRF = standard modifiable cardiovascular risk factors

STEMI = ST-segment-elevation myocardial infarction

WES = whole-exome sequencing

Coronary artery disease (CAD) claims >7.2 million lives per year globally and affects approximately 126 million individuals.[1,2] The 4 key standard modifiable cardiovascular risk factors (SMuRFs) of hypertension, dyslipidemia, diabetes mellitus, and smoking are crucial to identifying, targeting, and monitoring at the population level. However, an increasing proportion of individuals presenting with myocardial infarction (MI) have none of these individual factors, at least not reaching the current accepted thresholds for diagnosis and the initiation of primary prevention therapy. This proportion has been shown to be not insignificant and has risen at a steady and significant rate, from 11% in 2006 to 27% in 2014 of people presenting with ST-segment-elevation MI (STEMI) at a single Australian institution (**Figure 1A**), a trend confirmed in a national cohort study.[3,4] Globally, the proportion of people presenting with an acute coronary syndrome (ACS) event in the absence of SMuRFs is estimated to be 11.6%.[5] SMuRFless stable coronary disease and MI have substantial public health implications, with a conservative estimate of >1 million deaths globally from CAD in the absence of these risk factors.[1]

Although it may be assumed that these individuals have better outcomes than those who possess traditional risk factors, recent data suggest a greater complexity, and optimal management is unclear. In a study of the Australian GRACE (Global Registry of Acute Coronary Events) and CONCORDANCE (Cooperative National Registry of Acute Coronary Events) Registry cohorts of 3,081 participants, STEMI patients without SMuRFs were observed to have a higher in-hospital mortality compared to their counterparts with SMuRFs (6% vs 4%).[4] This finding was replicated in the larger Swedish national cardiac registry, SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies).[6] In this cohort of >60,000 STEMI patients (**Figure 1B**), women without SMuRFs presenting with a STEMI had a particularly high 30-day mortality of 19% compared to women with 1 or more SMuRFs (11%; $P < 0.0001$). A similar increase in mortality risk was seen in male patients without SMuRFs but with lower absolute rates consistent with the known poorer outcomes in women (10% vs 6%; $P < 0.0001$). The higher early mortality was at least partially

HIGHLIGHTS

- Patients with coronary atherosclerosis and myocardial infarction lacking modifiable risk factors face a high rate of early mortality.
- An evidence-based pathway has been introduced to guide the management of such patients.
- An international multicenter registry may provide insights leading to improved clinical outcomes.

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attributable to a lower rate of prescription of angiotensin-converting enzyme inhibitors, angiotensin receptor blocker, and beta-blockers in STEMI patients without SMuRFs, and it appeared to be driven by sudden arrhythmic death.

Stratification and analysis of SMuRFless patients in CAD and MI studies are effectively absent in the literature. Not a single clinical study of the 256 manuscripts referenced in the current European[7] and U.S.[8,9] guidelines identify the proportion of SMuRFless MI patients.[10] The reduced rates of guideline-directed pharmacotherapy received by people without SMuRFs post-STEMI and the mediating role this has on the group's early excess mortality[6] point to the importance of applying evidence-based therapies equitably. In the case of secondary prevention, until evidence is available suggesting otherwise, therapies targeting low-density lipoprotein cholesterol (LDL-C), the renin-angiotensin system, antiplatelets, and lifestyle measures should remain the same for people with CAD, both with and without SMuRFs. To improve the precision of these targets and management of SMuRFless CAD, we encourage clinical trialists to specifically identify this subgroup in their primary analyses to help unravel potential differential treatment effects and support future secondary analyses.

Although we await definitive trial evidence in people with CAD in the absence of SMuRFs, we provide herein clinical guidance that seeks to improve outcomes for this patient population. We assembled an international, multidisciplinary team and together established a clinical pathway for evaluation and management using a modified Delphi approach where clear evidence was not available for this population. The resulting consensus pathway recommends the following steps: 1) confirmation of underlying atherosclerotic disease; 2) true SMuRFless status of the individual; 3) current use of evidence-based secondary prevention; and 4) additional diagnostic tests for less typical, modifiable contributors to CAD, with interventions as appropriate. The development of the clinical pathway and the specialty clinics working toward implementation and measuring its impact for efficacy and cost-effectiveness are described later in this report. Such a dedicated pathway for this previously overlooked group of people with CAD and those presenting with an MI may improve outcomes for these individuals. Given that the excess mortality for SMuRFless MI patients is seen within the first 30 days, the recommendations have important relevance for clinicians caring for patients, particularly in the acute setting.

METHODS

APPROACH TO DEVELOPING A CONSENSUS CLINICAL PATHWAY. Our multidisciplinary, international team was awarded a National Health & Medical Research Council (Australia) Centre for Research Excellence (CRE) grant to develop evidence-based clinical pathways to improve the care of people with CAD without SMuRFs (grant number GNT1196629, "CRE for Better Outcomes in CAD"). Translation of research into outcomes within the CRE is based on the Promoting Action on Research Implementation in Health Services theoretical framework.[11] The framework has been used by many international studies to guide the application of research evidence into practice and proposes that implementation is dependent on the interplay between the robustness of evidence, context (culture, leadership, and collaboration), and process facilitation.

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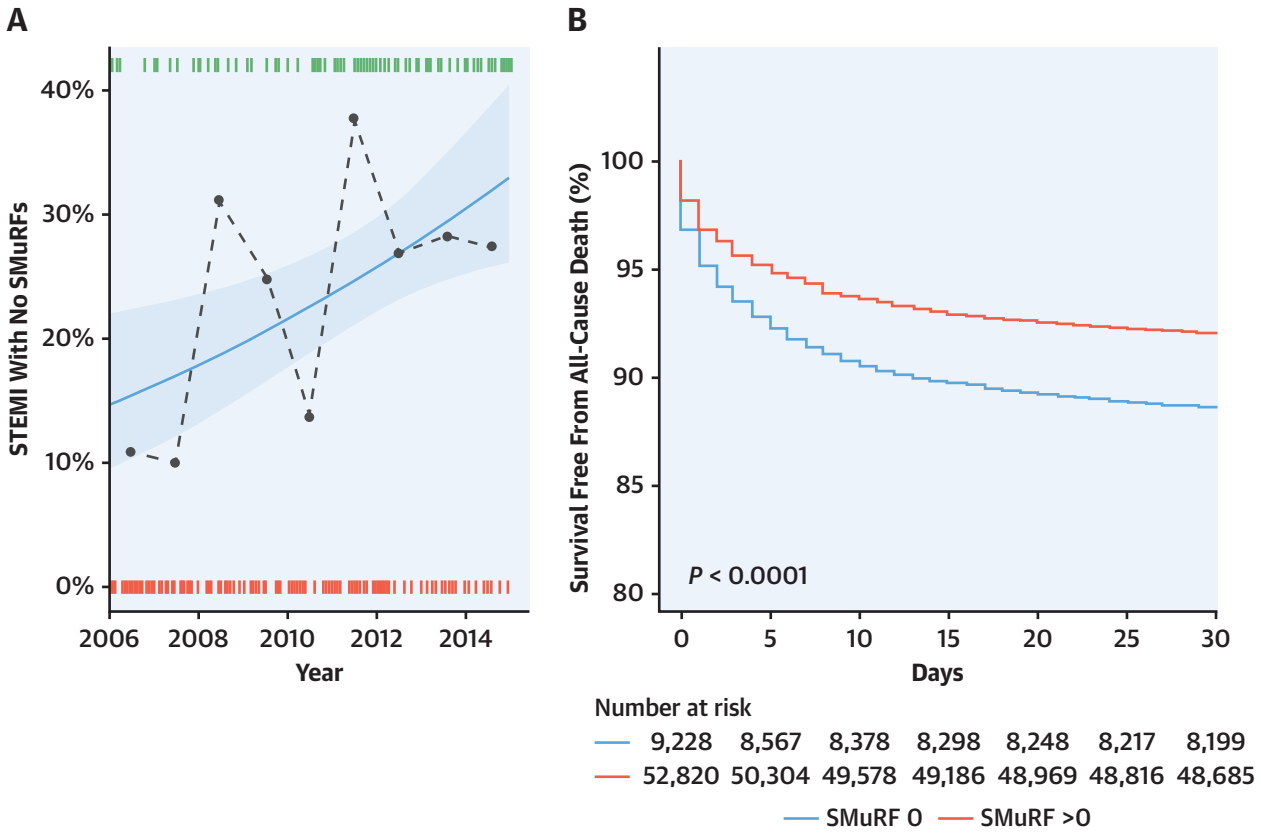
FIGURE 1 Proportion of SMuRFless STEMI Patients and All-Cause Mortality



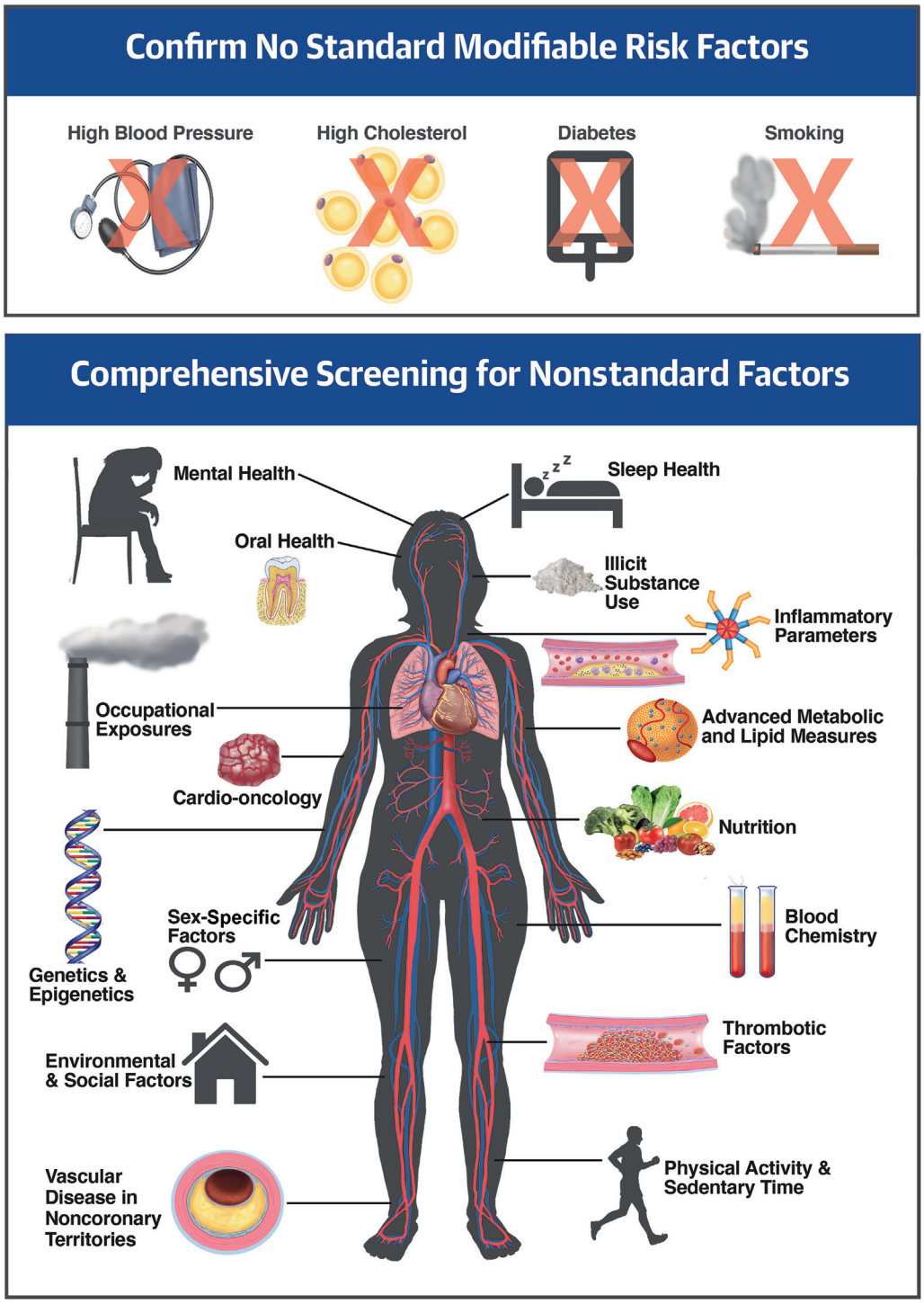
(A) Increase in the percentage of STEMI patients with no SMuRFs in a single-center study, Sydney, Australia ($P < 0.01$).[3] The **blue line** represents the regression fit using individual patient data, the **shaded area** depicts a pointwise 95% CI, and the **dotted lines** show average values per year. **(B)** Kaplan-Meier survival curves demonstrating excess mortality up to 30 days in SMuRFless **(blue line)** compared to >0-SMuRF **(red line)** STEMI patients in SWEDEHEART (The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) ($P < 0.0001$). Sex aggregated analysis from data included in the previous publication,[6] used with permission of the authors and data custodian. SMuRF = standard modifiable cardiovascular risk factor; STEMI = ST-segment–elevation myocardial infarction.

PANEL. An expert panel composed of 17 internationally recognized cardiovascular disease (CVD) leaders was asked to consider the design of the SMuRFless CAD clinical pathway. The panel included clinicians, researchers, health economic and policy experts, and patient representatives.

DATA. The expert panel was convened electronically (email and digital survey) 5 times between September 2020 and January 2021. Panel members were invited to contribute diagnostic investigations potentially relevant in this patient population to either: 1) confirm SMuRFless status; or 2) identify less frequent risk factors for coronary atherosclerosis initiation or progression (**Central Illustration**). Proposals for specific therapeutic decisions were also encouraged. The central team collated these suggestions into a database for future workshops.

PROCESS. Initially, a total of 46 items were proposed and considered by the expert panel. A 2-step modified Delphi method was then used to establish agreement on investigations to include in the clinical pathway and for whom. In round 1, expert panel members were asked to indicate whether each investigation was appropriate in the following categories: 1) clinically for all SMuRFless CAD patients; 2) clinically indicated in a moderate proportion; or 3) as a research tool only. Investigations that did not receive a majority of experts voting in 1 of the 3 categories were included in 2 additional electronic voting rounds after adjustment within the proposed pathway.

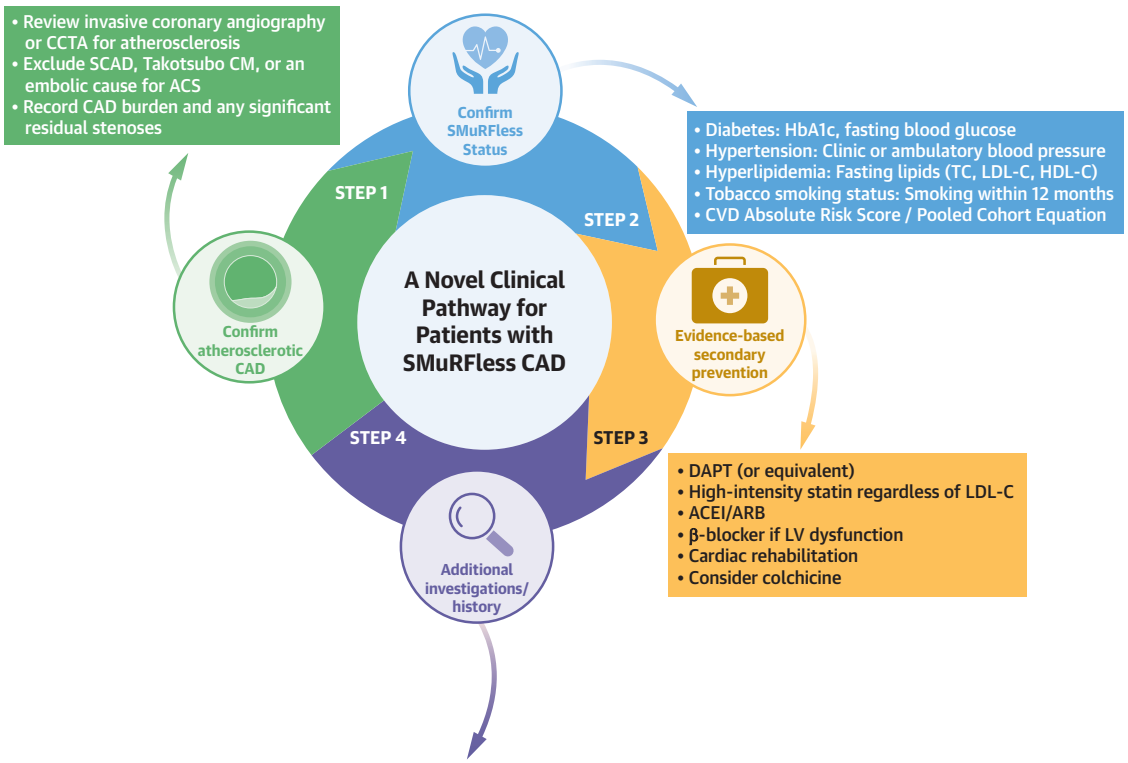
CENTRAL ILLUSTRATION **Diagnostic Considerations to Confirm No Standard Modifiable Cardiovascular Risk Factors, and to Screen for Nonstandard Factors**



Figtree GA, et al. J Am Coll Cardiol. 2023;82(13):1343–1359.

Less common risk factors for consideration in patients with coronary artery disease (CAD) in the absence of standard modifiable cardiovascular risk factors (SMuRFS) (hypertension, hypercholesterolemia, diabetes, and smoking) were identified by an international and multidisciplinary panel of cardiovascular disease experts. Dedicated clinical pathways and specialized clinics will ensure comprehensive investigation and evaluation of these factors in patients with SMuRFless atherosclerotic CAD as a novel strategy to optimize disease management and secondary prevention in this overlooked subgroup of the CAD population.

FIGURE 2 **SMuRFless CAD Clinical Pathway**



Blood biochemistry, advanced metabolic and lipid measures
- Renal function
- Liver function
- Thyroid function
- Lipoprotein(a)
- Fe studies, Vit D, Calcium, Magnesium, Phosphate
- Uric acid
- Glucose tolerance test
- Fasting insulin (HOMA scores)

Sleep, nutrition, physical activity, oral health
- Obstructive sleep apnea (OSA50) questionnaire
- Nutrition screening
- International Physical Activity Questionnaire
- Self Reported Oral Health (SROH) Questionnaire

Mental health and illicit substance use
- Medical history of mental health conditions
- Depression screening
- Medications for anxiety / depression and psychosis
- Use of recreational drugs (eg, cannabis, cocaine)

Inflammatory parameters
- Full blood count
- hs-CRP, ANA, ANCA, rheumatoid factor, anti-CCP Ab
- Known biomarkers (eg, IL-6, IL-1B, IL-18)
- Clonal hematopoiesis of indeterminant potential (CHIP)

Cardio-oncology
- History of past malignancy and therapies (eg, mediastinal radiation, chemotherapy, biologics/ immunotherapies)

Female specific
- History of pregnancy
- Hypertensive disorders of pregnancy (preeclampsia, gestational hypertension)
- Gestational diabetes
- Small for gestational age
- History of endometriosis, polycystic ovarian syndrome, ovarian insufficiency
- Menopause (premature or surgical)

Male specific
- History of erectile dysfunction, reduced libido
- Use of testosterone-replacement therapy
- Use of synthetic steroids

Thrombotic factors
- PT, APTT, fibrinogen, PAI-1
- Homocysteine
- Haptoglobin

Additional vascular studies
- Ambulatory BP
- Carotid duplex U/S and ankle-brachial index

Environmental, occupational and social factors
- Heavy metals (history ± blood levels)
- Education level, socioeconomic status
- Exposure to air pollution
- Tick IgE sensitivity to α-gal (history ± blood levels)

Genetics
- Rigorous family history on standardized family tree
- Polygenic risk score
- If suspicious of rare variant, whole exome or whole genome sequencing (with genetic counseling)

● All Patients ● If Clinically Indicated

Continued on the next page

Investigations considered to be research-only tools were removed from this clinical pathway.

RESULTS

THE SMuRFless CAD CLINICAL PATHWAY: INVESTIGATIONS AND MANAGEMENT. After review of existing evidence, as well as considering expert opinion where published evidence was unavailable, a clinical pathway was developed that outlines additional investigations and management that will be considered in patients with CAD without SMuRFs. Eighty-six percent of the components included in the final SMuRFless CAD clinical pathway received at least 75% support for their inclusion in the pathway. Nine components—including vitamin D, calcium/magnesium/phosphate, Self-Reported Oral Health Questionnaire, rheumatoid factor, anti-CCP antibody, PAI-1, ankle-brachial index, heart rate variability, and tick immunoglobulin (Ig) E sensitivity to α-galactose-1,3-galactose (α-gal)—received between 66.7% and 74.9% approval and were ultimately included in the final clinical pathway.

This diagnostic pathway will be implemented in National Health & Medical Research Council SMuRFless CAD specialty clinics, initially in 3 Australian states (New South Wales, Victoria, and South Australia) and incorporated into additional dedicated or broader CAD clinics where SMuRFless patients may be found, including in Singapore and Mount Sinai Health System, New York. It is encouraged for any physician managing a patient with CAD in the absence of SMuRFs. A schematic representing the steps and their components is shown in Figure 2, with further details provided in the following sections.

Step 1: confirm atherosclerotic CAD. First, the diagnosis of atherosclerotic CAD will be confirmed. In the case of a prior acute MI presentation, non-atherosclerotic etiologies—such as spontaneous coronary artery dissection, coronary artery embolism, and takotsubo cardiomyopathy—will be excluded because they each mandate a different diagnostic and treatment pathway. In patients with stable CAD, coronary computed tomography angiography (CCTA), or coronary artery calcium scoring can be used.

Step 2: confirm SMuRFless status. After atherosclerotic CAD is confirmed, an assessment of potentially missed or multiple subthreshold SMuRFs will occur. This allows for the identification of people in whom CAD is considered to have developed truly in the absence of SMuRFs or where the development of CAD is not clearly attributable or is out of proportion to mild elevation of SMuRFs and where there is likely benefit in investigating for additional modifiable factors.

Pragmatic and conservative cutoffs for the 4 risk factors are presented in Table 1. Multiple resting blood pressure (BP) measurements will be performed as well as a review of prior medical records. In most cases, unless the patient has a long-term record of low normal BP readings, a 24-hour ambulatory BP monitor is recommended. A diagnosis of hypertension will be established by: 1) an average reading of systolic BP of ≥140 mm Hg or diastolic BP of ≥90 mm Hg recorded from at least 2 readings obtained on separate days; 2) hypertension diagnosed by 24-hour ambulatory BP; or 3) ongoing treatment of hypertension. A standard fasting lipid panel will be obtained in all patients, including LDL-C. The use of LDL-C of >3.5 mmol/L for the SMuRF definition of hyperlipidemia is based on the cutoffs used in primary prevention guidelines for the commencement of lipid-lowering therapy. Fasting glucose and glycosylated hemoglobin levels will be measured in all patients. Diabetes mellitus is defined as a fasting blood glucose level of ≥7.0 mmol/L or glycosylated hemoglobin of ≥6.5% (48 mmol/L), as per the World Health Organization.[12]

Given the limitation of single binary thresholds for risk factors with linear associations with CVD risk, interactions among risk factors, and the potential for

FIGURE 2 Continued

A novel, evidence-based pathway for investigating the potential causes of atherosclerotic CAD in patients with no SMuRFs for improved clinical management and secondary prevention. A 2-step, modified Delphi method was applied to generate the pathway. Following confirmation of SMuRFless atherosclerotic CAD, historic and/or additional investigations **(step 4)** are required for all patients **(outlined in red)** or if clinically indicated **(outlined in purple)**. Created with BioRender.com. Ab = antibody; ACEI = angiotensin-converting enzyme inhibitor; ACS = acute coronary syndrome; ANA = antinuclear antibody; ANCA = antineutrophil cytoplasmic antibodies; APTT = activated partial thromboplastin clotting time; ARB = angiotensin receptor blocker; BP = blood pressure; CAD = coronary artery disease; CCP = cyclic citrullinated protein; CM = cardiomyopathy; CCTA = coronary computed tomography angiography; CVD = cardiovascular disease; DAPT = dual antiplatelet therapy; HbA1c = glycosylated hemoglobin; HDL-C = high-density lipoprotein cholesterol; HOMA = homeostatic model assessment for insulin resistance; Hs-CRP = high-sensitivity C-reactive protein; IgE = immunoglobulin E; IL = interleukin; LDL-C = low-density lipoprotein cholesterol; LV = left ventricle; PAI = plasminogen activator inhibitor; PT = prothrombin time; SCAD = spontaneous coronary artery dissection; SMuRF = standard modifiable cardiovascular risk factor; TC = total cholesterol; U/S = ultrasound; Vit D = vitamin D.

TABLE 1 Thresholds Used for the Definition of SMuRF/SMuRFless Status

Risk Factor	Definition for SMuRF Positive
Hypertension	SBP ≥140 mm Hg or DBP ≥90 mm Hg
Diabetes mellitus	HbA1c ≥ 6.5% or fasting BGL ≥7.0 mmol/L or OGTT 2-h BGL >11.1 mmol/L
Hypercholesterolemia	TC >5.5 mmol/L LDL-C >3.5 mmol/L
Cigarette smoking	Current smoker (smoking within 12 months)

BGL = blood glucose level; DBP = diastolic blood pressure; HbA1c = glycosylated hemoglobin; LDL-C = low-density lipoprotein cholesterol; OGTT = oral glucose tolerance test; SBP = systolic blood pressure; SMuRF = standard modifiable risk factor; TC = total cholesterol.

multiple risk factors at subthreshold levels to contribute to heightened CAD risk, the pooled cohort equation will be calculated during the clinic visit and contribute to the clinician's confirmation of SMuRFless atherosclerotic CAD.

Obesity has not been included as 1 of the 4 SMuRFs in the definition of SMuRFless CAD, but it is documented and is a potential modifiable factor that will be addressed in the clinical pathway.[13] This is because of the mixed evidence for diet-based weight loss as a therapy. Emerging evidence regarding the benefits of bariatric surgery on major adverse cardiovascular events (MACE) may shift this.[14] Of interest, studies have demonstrated lower body mass index (BMI) in SMuRFless ACS patients compared to their counterparts with SMuRFs, which may suggest that adiposity is not the main driver of advanced atherosclerosis in the SMuRFless cohort.[5] Ethnicity-based thresholds for BMI will be used, recognizing the inaccuracy and poor sensitivity of this measure correlating to high-risk body fat distribution across racially diverse populations.[15-19]

Step 2 will likely reveal a proportion of patients in whom SMuRFs had been "missed" or with results that are borderline and require further investigation. Additional commonly measured lipid parameters such as triglyceride/high-density lipoprotein cholesterol (HDL-C) will also be considered. In this scenario, appropriate diagnosis and management of the newly diagnosed risk factor will be pursued and is described, as appropriate, in step 4.

Step 3: confirm appropriate use of evidence-based secondary prevention. In accordance with treatment guidelines for patients with manifest atherosclerotic CAD, every effort will be made to ensure that patients receive guideline-based and evidence-based secondary prevention therapies, irrespective of their cholesterol and BP measures.[20-22] As more specific evidence evolves, including metadata from previous clinical trials, specific guidelines may emerge that particularly focus on the heightened susceptibility to disease and the vascular inflammatory response. Additionally, given the prevalence of SMuRFless ACS patients and their heightened early mortality, we advocate for intentional inclusion of SMuRFless CAD patients in interventional and secondary prevention trials because they are likely risk enhancers.

In the absence of any specific contraindications, appropriate antiplatelet therapy considering revascularization status, angiotensin-converting enzyme inhibitors/angiotensin receptor blocker, beta-blockers, and maximally tolerated statin therapy—with or without other lipid-lowering therapies—should all be prescribed according to guidelines.[20,23] Additional heart failure-targeted therapies (including mineralocorticoid receptor antagonists, sacubitril/valsartan, sodium-glucose cotransporter-2 inhibitors, and/or device therapy) will be considered when indicated.[24,25] Recent evidence suggests potential benefits of anti-inflammatory agents, such as colchicine for patients with both ACS and stable CAD, though more evidence is needed.[26,27] Further studies are required; however, the development of CAD in the absence of traditional cardiovascular risk factors may suggest an inflammatory process, and the use of anti-inflammatory agents may be particularly relevant to SMuRFless CAD patients.

Although the primary intention of the experts in developing this clinical pathway is to address potential modifiable components driving susceptibility to atherosclerosis and to ensure that secondary prevention is optimized, residual ischemia should also be considered and addressed according to current international guidelines,[28] taking into consideration the acute vs chronic nature of presentation, patient symptoms, and left ventricular function.

Step 4: pathway for investigating potential causes of SMuRFless CAD. The SMuRFless CAD clinical pathway has been designed to systematically screen for additional factors known to be associated with atherosclerosis, increased CVD morbidity, and mortality. A comprehensive clinical history that screens for cardiovascular and specific non-cardiovascular comorbidities (including liver, lung, or kidney disease; inflammatory disorders; endocrinopathies; hormonal or sex-specific factors; neurologic disorders; malignancy; chronic infections; and mental health disorders) as well as physical and hemodynamic factors (including BP, heart rate, height, weight, and waist and hip circumference) will be assessed. Details of evidence and recommended investigations are outlined in the following sections. Abnormal results from these investigations will precipitate referral to appropriate specialist physicians.

There is currently no hierarchy for these potential drivers; however, evidence from the proposed registry will be used to assess prevalence and impact of treatment and, thus, will guide prioritization of these factors in the future. Emerging evidence of new potential contributors or new assays will be considered by the CRE for CAD investigators for incorporation into the pathway on a biennial basis.

Obstructive sleep apnea. The hypoxemic and sleep fragmentation consequences of OSA are associated with altered cardiac and pulmonary vascular hemodynamics and have been shown to drive sympathetic activation, systemic inflammation (via a nuclear factor κB pathway), endothelial dysfunction, and generation of reactive oxygen species, which promote the development of atherosclerosis.[29,30] There is evidence for higher rates of incident CAD and excess MACE in patients with severe untreated OSA,[31] although OSA treatment has been disappointing with regard to protecting against MACE.[32] The prevalence of OSA in people with CAD without SMuRFs is not yet known but should be considered. All SMuRFless CAD clinic patients will initially be screened for OSA utilizing the OSA-50 questionnaire.[33] Patients with a significant OSA-50 score will be screened with a second tool, the Epworth Sleepiness Scale (ESS).[34] Patients will be referred directly for a home-based sleep study, according to Australian guidelines,[35] if OSA-50 and ESS screening results are both significant. Patients will additionally be referred to a sleep physician if indicated, with recognition of the development of the OSA-50 and ESS tools outside of CVD cohorts.

Nutrition. Dietary intake of fruit, vegetables, and fish will be considered along with measures of iron. Patients with poor diet should be provided recommendations, as per guidelines,[20,36] and potentially referred to a dietician. Counseling should include information about the benefits of consuming a Mediterranean or similar diet, replacement of saturated with unsaturated fat, increased consumption of plant-based foods rich in fiber, restricted consumption of processed meats, and consumption of fish.[37] Advice to reduce the consumption of sugary beverages and other forms of free sugar to <10% of total daily energy intake is recommended.[38] Guidance on daily sodium targets and reduction strategies will be provided. Counseling regarding optimal weight and calorie restriction approaches will be provided.

Physical activity. A detailed history of physical activity and sedentary time will be recorded for all patients using the International Physical Activity Questionnaire,[39] with continuous and categorical outcomes provided. Patients will be encouraged to adhere to a minimum amount of exercise, as per World Health Organization guidelines.[40] This includes at least 150 to 300 minutes of moderate-intensity aerobic activity or 75 to 150 minutes of vigorous-intensity aerobic physical activity throughout the week in addition to limiting the amount of sedentary time. Education programs, counseling, and the use of wearable devices to track and prompt activity will be considered to help optimize physical activity. Systematic reviews and meta-analyses support the benefit of increased physical activity with activity monitoring and prompts.[41-46]

Oral health and periodontal disease. Poor oral health has been associated with atherosclerotic CVD in several observational cohort studies[47-49] and will be considered. Periodontal disease is observed in 42% of the adult U.S. population.[50] An analysis of the 45 and Up study—a cohort of 267,153 men and women randomly sampled from the general population of New South Wales, Australia—revealed a relationship between increased risk of CAD and tooth loss, self-reported health of teeth and gums, and all-cause mortality.[51] A meta-analysis of 22 studies, including 129,630 participants, added further evidence, showing an approximately 2-fold increased odds of MI in those with periodontal disease after adjustment for traditional CVD risk factors.[52] Although causality is not certain and confounders may include lower education and socioeconomic status, a detailed history and examination are advised. All SMuRFless CAD clinic patients will be screened for periodontal disease using the 5-part Self-Reported Oral Health questionnaire[53] and referred to a dentist for further assessment if indicated. Maintenance strategies to ensure long-term improvements of oral hygiene[54] should be implemented in all patients as a cheap and accessible intervention strategy.

Psychological and social factors. Mental health and psychosocial risk factors have long been recognized for their association with risk of developing CAD and worse clinical outcomes, both via direct biological mechanisms and indirectly through common risk factors, environmental exposures, medication and substance exposures, and health behaviours.[55] Lower socioeconomic status[56,57] and tools measuring social isolation[58,59] have been associated with incident CAD and worse clinical outcomes, with varying degrees of interactions with traditional risk factors. Patients with depression have worse outcomes following a CVD event compared to nondepressed individuals, potentially in a dose-response relationship.[60,61] All SMuRFless CAD clinic patients will be screened to identify a depressive disorder with the Patient Health Questionnaire screening tool.[62] This questionnaire

relies on self-report and needs to be verified by a qualified clinician.

Inflammatory disorders. There is a well-established increased risk of CVD in those with systemic inflammatory conditions. These include systemic lupus erythematosus,[63] rheumatoid arthritis,[64] psoriasis,[65] and inflammatory bowel diseases.[66] Optimizing the treatment of inflammatory conditions, including using disease-modifying agents and targeted immunotherapy (eg, monoclonal antibodies), may reduce the incidence of CVD events in patients with inflammatory disorders.[67,68] A higher rate of ACS has been reported in people a year after recovery from COVID-19, and we await data on the extent to which this can be explained by standard risk factors[69]; a clinical history will include COVID-19 infection and vaccination status, which may be valuable for registry purposes, although this currently will not influence management.

All patients attending the clinic will be screened for chronic inflammatory disorders by taking a comprehensive medical history to identify inflammatory arthritides, connective tissue disorders, and inflammatory bowel disease, as well as the use of disease-modifying therapies. In addition, a limited set of screening tests targeting biological markers for disease activity or diagnosis of certain inflammatory conditions will be obtained, including high-sensitivity C-reactive protein, rheumatoid factor, anti-cyclic citrullinated protein antibodies, antinuclear antibody, and antineutrophil cytoplasmic antibodies. A more comprehensive panel of inflammatory markers should be undertaken if the clinical suspicion for an underlying chronic inflammatory disorder is high (based on history and clinical examination) or if the result of the initial biomarker screen described earlier is abnormal, with referral to a specialist physician if positive.

Cardio-oncology. A history of previous malignancy and management will be assessed and documented in all SMuRFless CAD clinic patients, with a particular focus on childhood malignancy; mediastinal radiation; and chemotherapy agents, immunotherapies, and biologics.[70-72]

Sex-specific factors. There is growing evidence in support of assessment for sex-specific factors associated with increased CVD risk in women and men.[73] Factors that will be considered in the SMuRFless CAD clinic include features of pregnancy (pre-eclampsia, small for gestational age, preterm birth, gestational hypertension, gestational diabetes, maternal pre-existent type 1 or type 2 diabetes),[74-77] sex hormones (endometriosis, polycystic ovary syndrome, ovarian insufficiency),[78,79] menopause/hormonal status, and use of hormone contraceptives. Male-specific factors that are associated with increased risk of CAD include androgen deficiency,[80] erectile dysfunction,[81] and use of anabolic or synthetic steroids.[82] All participants will be screened for such potential sex-specific contributors through history, examination, and potential additional investigations where relevant.

Metabolic and vascular health. If the standard measures of metabolic health in step 2 detect any abnormality or are borderline, fasting insulin and glucose levels will be measured in people attending the SMuRFless CAD clinic, and homeostatic model assessment for insulin resistance and homeostatic model assessment of beta-cell function scores will be calculated. The use of glucose tolerance tests (>4 weeks post-ACS, to avoid false-positive results) will also be considered by the clinician, with referral to endocrinology specialists as relevant. In addition to standard fasting lipid levels, lipoprotein(a) will be measured in all patients. Non-HDL-C will be calculated and reviewed as an alternative marker, with consideration of the role of atherogenic particles in complex settings, such as hypertriglyceridemia and diabetes, chronic kidney disease, and metabolic syndrome.[83]

Thrombotic factors. Abnormalities in clotting and fibrinolysis may contribute to both the development of atherosclerosis and risk of an acute arterial thrombotic event, although specific management may not be clear if abnormalities are identified. Such measures should be taken >4 weeks post-ACS (and in the absence of acute infections) to assess baseline levels rather than acute phase reactants.

Fibrinogen binds to platelets via glycoprotein IIb/IIIa receptors, promoting platelet aggregation in addition to contributing to blood viscosity, and it is an independent risk factor for CVD.[84-86] Fibrinogen levels and activity may mediate the effect of some traditional CVD risk factors, with higher fibrinogen antigen and activity seen in association with age, smoking, diabetes, BMI, total cholesterol and triglyceride levels, and lower levels with increasing HDL-C.[87]

Plasminogen activator inhibitor (PAI)-1 is the main physiologic inhibitor of tissue-type and urokinase-type plasminogen activator, which are responsible for the enzymatic activation of plasminogen and, thus, are required for the dissolution of insoluble fibrin in clots. Polymorphisms in the promoter are associated with altered plasma PAI-1 concentrations and are associated with CAD.[88] PAI-1 antigen levels,

but not activity, are associated with increased MACE.[89]

Homocysteine is an intermediary molecule in the biosynthesis of methionine and cysteine, predominantly found in the circulation bound to plasma proteins. Hyperhomocysteinemia, which may arise from genetic mutations to enzymes including cystathionine-β-synthase and homozygous mutations in methylenetetrahydrofolate reductase, have been associated with premature CVD events.[90] Hyperhomocysteinemia can also result from nutritional deficiencies in folate, vitamin B12, and vitamin B6 and with metformin therapy (via reduction in B12 levels). Homocysteine is renally cleared and is elevated in patients with chronic renal impairment, which provides one of several potential mechanisms for increased rates of CVD in patients with renal disease. Several observational studies have shown an association between homocysteine levels and coronary events.[91] Measuring homocysteine levels, along with other nutritional factors, such as B12 and folate, may provide additional insights into mechanisms, with the caveat that a systematic review and meta-analysis of intervention studies reducing homocysteine levels did not show a reduction in MI, stroke, or mortality. The potential role of homocysteine in SMuRFless CAD patients remains unknown and will be reconsidered as additional data become available.[92]

Haptoglobin is a glycoprotein produced by the liver that binds to free hemoglobin in blood, thereby mediating its removal from the circulation and preventing oxidative damage to tissues. Haptoglobin has 2 alleles (Hp-1 and Hp-2). The Hp-2/Hp-2 homozygous phenotype is associated with an increased risk of MI, stroke, and CVD mortality,[93-95] possibly through differences in antioxidant potential. In addition, haptoglobin appears to directly inhibit the oxidation of LDL-C, a key step in the pathogenesis of atherosclerosis.

Fibrinogen, PAI-1, and homocysteine will be measured in all SMuRFless CAD clinic patients. Haptoglobin may be considered in some patients.

Additional vascular studies. Screening for clinically significant atherosclerosis in other vascular territories will be considered in all SMuRFless CAD clinic patients, including carotid and vertebral artery atheroma using duplex Doppler ultrasound and peripheral artery disease in the lower limbs using ankle-brachial index if symptoms are suggestive of clinically relevant disease. Patients may be referred for lower limb arterial ultrasound assessment and referred to a vascular surgeon when appropriate. The burden of atherosclerotic CVD in noncoronary vessels in the absence of standard modifiable risk factors is currently unknown.

Environmental factors. The increased proportion of people post-STEMI without SMuRFs may be linked to increased exposure to environmental factors with a known or potential association with CAD.[4] Though patients will have been screened for history of tobacco smoking, significant exposure to passive tobacco smoke is a potential factor for the development of premature atherosclerosis[96,97] and will be considered in all SMuRFless CAD clinic patients.

Population-level data have pointed to an association between heavy metal exposure and atherosclerotic CVD.[98] Heavy metal chelator treatment has been shown to reduce CVD events in those with prior events,[99] which strengthens the level of evidence for a causal association. Exposure to common tick bites may sensitize the bite recipient to the development of IgE antibodies to mammalian α-gal.[100] At high levels, this leads to a hypersensitivity reaction to mammalian red meat. At more moderate levels, elevated α-gal IgE levels are associated with >2-fold risk of obstructive CAD[101] and are more pronounced in patients presenting with ACS than those with stable CAD.[101]

Potential environmental contributors to be investigated in all patients include exposure to heavy metals (lead, cadmium, mercury, and arsenic) and particulate air pollution,[102] collected by a history and/or direct measure. IgE sensitivity to α-gal will be considered in some patients with potential tick exposure history.

Inherited risk, genetic analysis, and polygenic risk scores. Genetic testing will likely be of limited direct benefit to those with known CAD based on the present evidence because guideline-directed medical therapy should be offered regardless.

Because of recent advances in biotechnology and high-throughput sequencing platforms, several options for genetic testing are available; however, they currently remain at a direct cost to the consumer. These including whole-genome sequencing (WGS), whole-exome sequencing (WES), single-nucleotide polymorphism array, with derivation of a polygenic risk score (PRS).

Several studies have shown that PRS performs well compared to traditional risk factors in univariate prediction of risk and augments the C-statistics of traditional risk factors taken as a whole. It can be implemented at minimal cost.[103,104] An index patient with SMuRFless CAD with high PRS may lead to the identification of family members where a high PRS may guide the individual's choices regarding lifestyle

and behaviors associated with improved CVD health as well as heighten adherence to primary prevention pharmacotherapy (particularly statins).[105] The identification of family members with high PRS may additionally allow the clinician to recommend a coronary artery calcium study to delineate coronary atherosclerotic burden or to establish more aggressive treatment targets or personalize secondary prevention approaches, given that PRS predicts relative and absolute benefit of LDL-C lowering.[106-109] It is important for interpretation and action with regard to PRS to consider patient ethnicity and the population in which the specific algorithm was developed.

All SMuRFless CAD clinic patients will be screened for a family history of CAD, which is typically defined as an MI, stroke/transient ischemic attack, or peripheral artery disease in a first-degree relative who had an event before the age of 55 years if male or 65 years if female. A family pedigree will be obtained, including second-degree relatives, which will help to guide consideration of genetic testing for inherited risk. In cases where a strong family history of premature and SMuRFless CAD is evident, screening for rare variants will be considered using whole-genome sequencing, WES, or single-nucleotide polymorphism array.[110] It is important to note that in the SMuRFless CAD setting where severe hypercholesterolemia is not present, genomics studies are not the clinical standard of care and would be performed on a research basis. Appropriate genetic counseling will be provided because of the implications of genetic testing on inherited risk in family members.

WES or targeted sequencing provides an opportunity to identify patients attending the SMuRFless CAD clinic with clonal hematopoiesis of indeterminate potential (CHIP), which is defined as the presence of an expanded somatic blood cell clone in persons without other hematologic abnormalities.[111,112] This relatively common finding has been associated with nearly a 2-fold increase in CAD in humans.[113] Strategies interrupting key inflammatory pathways may mitigate CHIP-associated CAD risk.[114-118] This may become increasingly relevant as clinical trials examine the efficacy of targeting CHIP with novel therapies.

DISCUSSION

IMPLEMENTATION OF AN INTERNATIONAL REGISTRY. To study and improve the potential utility and scalability of the SMuRFless CAD clinical pathway, a multicenter, prospective, observational patient registry has been established (ACTRN12622000452796). All patients receiving care in the SMuRFless CAD clinics across international sites will be invited to participate. In Australia, patients will be invited to provide informed consent for Medicare Benefits Schedule/Pharmaceutical Benefits Scheme data linkage, providing 5-year clinical outcomes data and facilitating analyses of the cost-effectiveness of the specialty clinic design. Patient-reported outcome measures and experience have also been incorporated.

SMuRFless CAD clinic patients will be offered the opportunity to participate in the BioHEART (Cardiology Biobanking for Biomarker Discovery; ACTRN12618001322224) cohort study.[119] The BioHEART study invites participants to provide blood samples, clinical and imaging data, and permission for linked outcome data collection. Here, deep molecular phenotyping with candidate and multiomic technologies will be performed, with machine learning efforts used to identify residual mechanisms of CAD susceptibility and resilience.

As evidence emerges regarding novel risk factors, treatment patterns, and biomarkers in this population, testing in controlled interventional study settings will be required. The SMuRFless CAD Registry is planned to serve as a mechanism to efficiently engage well-phenotyped, appropriate individuals who have indicated that they wish to be contacted for future research opportunities regarding new interventional studies or itself as a platform for embedded implementation studies and clinical trials. This may be particularly relevant to pathways involved in individual susceptibility to atherosclerosis, such as inflammatory and redox pathways, and novel targets that emerge from unbiased discovery “omic” studies.

COST-EFFECTIVENESS. There is currently insufficient data available to assess the cost-effectiveness of recommendations within this clinical pathway to screen for the nonstandard risk factors. To begin to address this important issue, we plan to perform health economic analyses incorporating prevalence and outcome data collected in the proposed national registry, together with data from randomized trials when available.

STUDY LIMITATIONS. This document presents an expert opinion consensus clinical pathway for the evidence-based management of patients with atherosclerotic CAD in the absence of SMuRFs. We considered all of the levels of evidence available and acknowledge that, in many cases, high-level evidence

is lacking. There is much opportunity to refine this pathway as more evidence becomes available. We advocate for the implementation of a multicenter global registry to provide further insights into the appropriate management of SMuRFless CAD patients and a platform for embedded implementation studies and clinical trials.

CONCLUSIONS

Patients with SMuRFless CAD are being increasingly recognized for their prevalence and their specific unmet needs. They are, as a subgroup, not visible in clinical trials or guidelines. Here, we have provided a comprehensive review of current evidence and, where evidence is not available, expert opinion regarding the management of CAD in patients without SMuRFs. Adherence to current guidelines for acute MI management and secondary prevention is recommended but is currently suboptimal according to large registry data. This disparity in guideline-based care for SMuRFless MI patients is a significant contributor to their heightened early mortality. Dedicated clinical pathways and specialized clinics will ensure that people with CAD without SMuRFs receive personalized, evidence-based secondary prevention, agnostic to SMuRFless status, and, in some cases, specialized diagnostic tests for potential modifiable contributors to CAD. The related SMuRFless CAD Registry will provide ongoing data to improve practice and will provide a platform for embedded clinical trials of novel therapeutic strategies targeted at these individuals.

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KEY WORDS atherosclerosis, cardiovascular risk, clinical pathway, coronary artery disease, primary prevention, secondary prevention

APPENDIX For a list of the CRE for CAD Collaborators, please see the online version of this paper.