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The Management of Stable Angina in the Older Adult Population

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Abstract

As society ages, the number of older adults with stable ischemic heart disease (SIHD) continues to rise. Older adults exhibit the greatest morbidity and mortality from stable angina. Furthermore, they suffer a higher burden of comorbidity and adverse events from treatment than younger patients. Given that older adults were excluded or underrepresented in most randomized controlled trials of stable ischemic heart disease, evidence for management is limited and hinges on subgroup analyses of trials and observational studies. This review aims to elucidate the current definitions of aging, assess the overall burden and clinical presentations of SIHD in older patients, weigh the available evidence for guideline-recommended treatment options including medical therapy and revascularization, and propose a framework for synthesizing complex treatment decisions in older adults with stable angina. Due to evolving goals of care in older patients, it is paramount to readdress the patient's priorities and preferences when deciding on treatment. Ultimately, the management of stable angina in older adults will need to be informed by dedicated studies in representative populations emphasizing patient-centered endpoints and person-centered decision-making.

SUBJECT TERMS:

Coronary Artery Disease; Angina; Percutaneous Coronary Intervention; Revascularization; Aging

Keywords

Stable angina; Percutaneous coronary intervention; medical therapy; chronic coronary syndrome; stable ischemic heart disease; older adults

INTRODUCTION

Stable ischemic heart disease (SIHD) is a key contributor to morbidity, mortality, and disability in older adults.[1] Older adults ≥75 years old make up 30% of patients with

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SIHD with more than three million older Americans impacted.[1,2] Multiple randomized controlled trials (RCTs) and current guideline recommendations support that most patients with SIHD and stable clinical features can be initially managed with medical therapy[3–8], with revascularization indicated in patients with breakthrough symptoms and in those with high-risk anatomy. As symptom control is the primary goal of management, this presents unique challenges for clinicians owing to the higher prevalence of multimorbidity in older adults with competing conditions, polypharmacy concerns, and variable goals and priorities of care; all of which can influence both symptoms and quality of life.[9–11] Given this complexity, the aim of this contemporary review is to evaluate the definition of aging for clinical and research purposes, discuss the overall burden and clinical presentation of stable angina in older adults, introduce a framework for initial medical and subsequent invasive treatment options, and delineate key future areas for investigation.

I. How Do We Define “Older” For Clinical and Research Purposes?

In less than two decades, the number of older adults is expected to overtake the number of children for the first time in US history.[12] As the US and global population ages, the definition of an “older adult” has shifted. In the U.S., older adults have traditionally been defined as adults ≥65 years based on the standard retirement age, which was an arbitrary cutoff deemed acceptable for economic stability in the early 1900s. However, as medical care improved over decades, many adults aged ≥65 years have remained active and healthy, especially those <75 years old. In fact, remaining life expectancy at age 75 in 2007 was similar to life expectancy at age 65 in 1950[13], and hence the use of the traditional retirement age as a cutoff for older adults has become increasingly anachronistic. Given this changing landscape, older adults have been classified as age ≥75 years in recent studies of cardiovascular diseases.[14–16] Future improvements in health care will continue to raise questions regarding how to optimally define this growing and diverse population.

Furthermore, clinicians and scientists are becoming increasingly aware that chronological age should be interpreted in the context of “biological” age, or the functional and physiologic changes that occur over time in an individual, which can vary greatly between people despite the same chronological age.[17] There are many proposed predictors of biological age including epigenetic, telomere length, transcriptomic, proteomic, metabolomic, and composite biomarker predictors.[18] Predictors of biological age may provide equal or greater prognostic ability than chronological age.[19] Furthermore, geriatric syndromes, including frailty, multimorbidity, polypharmacy, and sarcopenia, may be useful surrogates for overall biological aging and serve as a reflection of the microscopic predictors of aging that may not be as readily captured or appreciated.[20] Geriatric syndromes also have important implications for outcomes following invasive cardiovascular procedures including percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG).[21] Ultimately, a clear understanding of a patient’s relative biological age may inform clinical decision-making, including evaluating risks and benefits of potential therapies, while also fostering enrollment of representative aging populations in clinical trials. Figure 1 highlights the heterogeneity of biological age at a given chronological age and numerous measures of biological aging for clinicians and researchers to consider when evaluating the older adult population.[19] Looking forward, using predictors of biological age alongside chronological age should consolidate understanding of the aging process and generate a more precise definition of “older” adults.

II. The overall burden and clinical presentations of SIHD in older patients

Also frequently referred to as chronic coronary syndrome and stable angina, SIHD is a major contributor to morbidity, mortality, and disability among older adults.[1,2] Some have estimated that nearly a quarter of individuals 75–79 years old and nearly a third of those ≥80 years old are living with coronary artery disease (CAD),[22] and the number of older adults living with SIHD is only expected to rise further. This is particularly troubling given that older adults experience the highest mortality and morbidity attributable to SIHD.[2] Notably, SIHD is a major contributor to disability and functional impairment, impacting mobility and management of instrumental activities of daily living,[23] and serves as a more powerful predictor of future disability than acute myocardial infarction (AMI).[24] Given this large disease burden, a clear understanding of the unique considerations around clinical phenotypes, potential tradeoffs of management, and goals of care in older adults with stable angina is crucial.

Clinical phenotypes—The assessment and interpretation of symptoms in older adults with SIHD can be challenging. Older adults most commonly present with chest pain or pressure as their primary anginal equivalent, but may also present with additional symptoms including dyspnea on exertion, nausea, epigastric or back discomfort, and fatigue.[25] Further complicating the interpretation of symptoms in patients presenting with obstructive CAD and ischemia is that multiple chronic conditions are exceedingly common among older adults living with CAD, with CAD commonly occurring concurrently with arthritis, diabetes, malignancy, depression, renal insufficiency, stroke, and chronic lower respiratory disease, among other conditions.[26] Symptoms of SIHD in older adults such as dyspnea and fatigue frequently overlap with symptoms attributable to non-cardiac conditions common in older adults, such as chronic lung disease, malignancy, anemia, frailty, depression, and chronic kidney disease.[27] This has important implications for therapeutic expectations for patients and clinicians. Figure 2 presents different clinical phenotypes potentially encountered in older adults with SIHD, with examples of common symptoms of stable angina seen in older adults and both cardiac and non-cardiac clinical comorbidities that may influence both symptomatic burden and response to treatment.

III. Weighing treatment options for older adults with SIHD including medical therapy, PCI, and CABG

Medical Therapy for Symptom Control in Older Adults with SIHD—Based on randomized trial evidence, we agree with current American and European guideline recommendations, which support an initial medical therapy approach with antianginal treatment in most patients with stable angina, including older adults, with revascularization primarily reserved for patients with unacceptable angina despite medical therapy.[3–8,28] Because older adults are less likely to undergo revascularization and more likely to receive incomplete revascularization,[29] a firm understanding of the risks and benefits of antianginal medications in older adults is a priority.

Beta-blockers and calcium channel blockers are recommended as first- and second-line agents respectively by the current U.S. guideline and as first-line agents by the European guideline.[8,30] Beta-blockers reduce ischemia by decreasing heart rate and blood pressure with activity, which can delay the onset of symptoms.[31] Calcium channel blockers increase coronary blood flow by decreasing coronary vascular resistance via dilation of both the epicardial and arteriolar vasculature, which leads to improvements in angina and exercise tolerance.[31] A limitation of the available evidence supporting the use of beta-blockers and calcium channel blockers is the older age of studies, many of which were nonrandomized, and the majority of which failed to include representative populations of older adults with multimorbidity, frailty, and other age-associated risks.[32–35] For example, prior studies comparing beta-blockers versus calcium channel blockers enrolled younger populations (mean age of 57 years),[35,36] with the largest randomized trial of beta blockers versus calcium channel blockers for stable angina with longer-term follow-up actively excluding septuagenarians and beyond.[36] More recent studies assessing these agents have been non-randomized and did not specifically report outcomes stratified by age.[37,38] Importantly, both agents present considerations for tolerability, adherence, and persistence, which can impact quality of life. Beta-blockers may contribute to dizziness and fatigue, bradycardia, sleep disturbances, and sexual dysfunction, with risk of cognitive and functional decline in some older patients.[39] Calcium channel blockers may cause constipation, bradycardia, and lower extremity edema in older adults, with effects varying across subclasses.[40] A key consideration is how symptoms possibly attributed to SIHD, such as dyspnea and fatigue, can be paradoxically exacerbated by certain antianginal therapies depending on the underlying etiology of those symptoms.

Beyond beta-blockers and calcium channel blockers, both short- and long-acting nitrates are a staple of many patients' antianginal regimen. Since their first use reported by Thomas Lauder Brunton in the 1800s, nitrates have the longest track record of safety and efficacy for the treatment of stable angina.[41] Both short- and long-acting nitrates improve exercise tolerance and delay the onset of symptoms in patients with stable angina, and older studies suggest similar efficacy to both beta-blockers and calcium channel blockers.[8,35,41] Reflecting these data, long-acting nitrates are recommended as second-line agents by the current guidelines[8,30] Significant limitations of nitrate treatment are headaches which can lead to non-adherence and discontinuation of therapy, as well as tachyphylaxis.[42] Nitrates should not be used in certain circumstances more common in older populations, including severe aortic stenosis and in patients taking phosphodiesterase inhibitors. Importantly, many of the commonly used antianginal medications, including beta-blockers, calcium channel blockers, and nitrates, may lead to hypotension, which can result in dizziness, syncope, and potential falls. Reassuringly, the available evidence does not demonstrate an increased risk of falls with these medications, although these were limited to observational studies.[43,44]

Beyond the first- and second-line agents described above, additional options may be considered for the treatment of refractory angina. Ranolazine is a selective inhibitor of the late inward sodium current and reduces angina and the need for sublingual nitroglycerin. One meta-analysis of randomized controlled trials comparing the efficacy of antianginal therapies in patients with stable angina refractory to initial treatment found that ranolazine added to either a beta-blocker or calcium channel blocker demonstrated benefits in exercise tolerance, angina frequency, and nitrate use.[45] However, prior studies have been limited to younger populations in their 60s with limited inclusion of older adults.[46] While generally well-tolerated, ranolazine can cause dizziness, nausea, constipation, and QTc prolongation, all of which have particular relevance among older adults.[30] Ivabradine is another antianginal agent that works via inhibition of the funny current, with modest evidence supporting its use for symptom control in patients with stable angina.[47] Additional agents recommended by the European guidelines, such as nicorandil and trimetazidine, are not approved for use in the United States.[30] Since most antianginal agents reduce blood pressure to some degree, clinicians must exercise caution when using these medications alongside other drugs which are known to lower blood pressure and cause orthostasis, a situation common in older patients with multiple comorbidities. Furthermore, cardiac rehabilitation is an excellent option for older adults with SIHD who are considering initiating an exercise regimen, with associated improvements in QoL, risk of hospitalization, and cardiovascular mortality.[48] While planning is required for older adults with stable angina considering an exercise regimen, with attention to competing conditions and pharmacotherapeutics, older adults with SIHD can achieve the same health benefits from aerobic, strengthening, and stretching exercises as younger populations.[49] While not often considered as directly related to symptom control, lifestyle changes and additional preventive interventions such as lipid-lowering therapies, eating a healthy diet, and smoking cessation, play a crucial role in the management of patients with SIHD.[30,50–52]

Percutaneous and Surgical Revascularization in Older Adults with SIHD— When compared to optimal medical therapy alone, the appropriate role for revascularization in SHID has been an area of active debate. Many SIHD trials were conducted before the widespread use of contemporary treatments and excluded patients ≥75 years of age with complex risk profiles, including those with multimorbidity, anatomic complexity, physiologic derangement, and geriatric syndromes. While trial evidence from younger and less complex cohorts suggest that revascularization may positively influence certain cardiovascular events versus medical therapy alone over time,[53–56] these trials did not demonstrate a survival benefit with percutaneous revascularization when compared to medical therapy alone (Table 1).[5,7,57,58]

In contrast, among patients with left main, complex multivessel anatomy with diabetes mellitus, and left ventricular dysfunction, surgical revascularization can provide both symptom relief and long-term survival benefits.[73] However, extrapolation to the older adult population with SIHD remains problematic because participants in these trials were younger with less complex disease and lower burden of geriatric syndromes than what is seen in clinical practice.[53,71–74] In older patients with higher surgical risk or with geriatric impairments, percutaneous revascularization is a reasonable alternative for left main or multivessel disease if the anatomy is suitable to provide reasonable relief of symptoms and improvement in quality of life.[73] Patients potentially benefitting from percutaneous options include those who had a prior CABG with a patent left internal mammary artery, advanced physical frailty, high multimorbidity burden, cognitive or physical dysfunction, the absence of good bypass targets, poor feasibility for complete revascularization, and patient-related preferences.[75] PCI in older adults is more complex than younger counterparts owing to their increased risk for procedural complications. Reasonable strategies to minimize risk include the routine use of radial artery access with up to 7F sheaths and guide-catheters, minimizing subtherapeutic or supratherapeutic anticoagulation during PCI, use of clopidogrel over more potent P2Y12 inhibitors, use of intravascular imaging for optimal stent deployment, plaque modification in the presence of severe calcific disease, and minimizing the need for large bore vascular access to introduce mechanical support devices. While mechanical support devices can assist hemodynamic stability for complex PCI, there is a higher risk of bleeding and vascular complications associated with these devices and implementation of vascular safety bundles to minimize such risks are necessary.[76]

The management of SIHD and revascularization strategy should take into account other therapeutic goals including reduction in angina or anginal equivalent symptoms, improvement in quality of life, and functional independence within age-related contextual factors.[77] Steps to standardize the approach for the decision to proceed with the optimal revascularization strategy are critical to reduce the iatrogenic risks from both surgical or percutaneous revascularization. When discussing the approach to revascularization, clarity on each older patient's functional capacity (physical and cognitive), frailty burden, comorbidities (including the use of the Charlson Comorbidity Index),[78] personal goals, and medication profiles are needed prior to intervention.[79] Non-invasive cardiac imaging may be helpful to quantify the degree of ischemia, particularly in the context of atypical symptoms, and mitigate biases of under- or over-diagnosis. Because older patients are at the greatest risk for procedural complications, *a priori* discussion on efforts to reduce these risks must be emphasized by the Heart Team. The optimal duration of antiplatelet therapy or other adjunctive therapies after percutaneous revascularization in older adults should also be considered to balance the tradeoffs between therapeutic benefits versus bleeding and other medication-related risks.[27] This balancing act is especially pertinent in patients with atrial fibrillation, which is common in older adults, and in whom anticoagulation will also need to be considered in addition to antiplatelet agents after revascularization. The AUGUSTUS trial showed that clopidogrel and apixaban may be safer than triple therapy after PCI, and there was no significant interaction between age and the primary outcome of major or clinically relevant nonmajor bleeding (p=0.675).[80] However, whether these data in patients after ACS can be extrapolated to patients with stable angina is unclear.

IV. Putting it all together

Without any mortality difference between invasive and medical therapeutic approaches, and assuming additional conditions are not present that favor one therapy over another, patients and their clinicians must prioritize strategies to optimize symptomatic improvement within the context of individualized goals for older patients. Further compounding this complexity are the potential contributions from competing chronic conditions that can influence response to therapies: depending on the primary source of the patient's concerns, symptom burden may be improved or paradoxically exacerbated with common cardiovascular treatments. Treatment strategies must be considered within the broader context of overall quality of life and the individual patient's priorities, preferences, and health goals. While maintenance of function and independence are a top priority for most older adults, very little is known about the impact of available treatments for SIHD on many of the outcomes that matter most to this population.[81] If an older adult presents with stable angina and fatigue, will a beta-blocker improve or worsen their quality of life? If an older patient presents with dyspnea on exertion and SIHD in the context of comorbid anemia and malignancy and prioritizes maintaining their activity level, will PCI and treatment with long-term dual anti-platelet therapy provide durable symptom improvement or have the opposite effect? Clinicians and patients are frequently faced with this uncertainty and, while many of these decisions lack a clear answer, an appreciation of the multitude of potential cardiovascular and non-cardiovascular factors at play may inform a trial-and-error approach. Thus, we propose a “Consider, Listen, Decide” framework for synthesizing these multiple considerations in older adults with stable angina (Figure 3).

Future Directions—In response to the limited evidence around many of the available therapies for SIHD in older adults, multiple calls for inclusion of representative populations of older adults with multiple chronic conditions have occurred over the years.[22,82,83] The National Institutes of Health Inclusion Across the Lifespan policy went into effect in January 2019, necessitating greater inclusion of representative populations of older adults in clinical trials. Prospective trials of available therapies on patient-centered outcomes for symptomatic SIHD in older adults are imperative to establish a firm evidence-base for treatment in this unique population. One such study is the recently PCORI funded Trial Comparing the Effectiveness and Tolerability of Medications in Older Adults with Stable Angina and Multiple Chronic Conditions: LIVE BETTER, which aims to determine the optimal first-line antianginal treatment strategy in older adults living with stable angina and multiple chronic conditions, with a focus on patient-centered outcomes such as quality of life, symptom control, and mobility. There is an urgent need for pragmatic trials that enroll older adults ≥75 years of age with SIHD to evaluate the efficacy and safety of revascularization strategies for patient-centered outcomes in older adults. While the historical clinical paradigm for treatment of stable angina has focused on the treatment of obstructive epicardial CAD, ischemia with non-obstructive coronary arteries (INOCA) has been increasingly recognized as a crucial contributor to the patient population presenting with stable angina. The literature is limited on epidemiology and management of INOCA among older adults, with the CorMicA (CORonary MICrovascular Angina) trial having a mean age of 61 years.[84] The iCorMicA trial will expand upon the initial pilot study with a broader patient population and the ongoing Women’s Ischemia Trial to Reduce Events in Non-obstructive Coronary Artery Disease (WARRIOR) Trial will include approximately one-third adults ≥65 years, both of which should help inform the management of older adults with INOCA.[85] The development and integration of geriatric-centric risk models and measures into clinical practice has the potential to better inform health trajectory and both patient and clinician expectations around treatment. Finally, patients with stable angina often misunderstand the potential risks and benefits of therapy, including believing that PCI will extend their lifespan.[86] Thus, the development and validation of new approaches to facilitate effective communication regarding benefits and tradeoffs of potential treatments must be a priority going forward.

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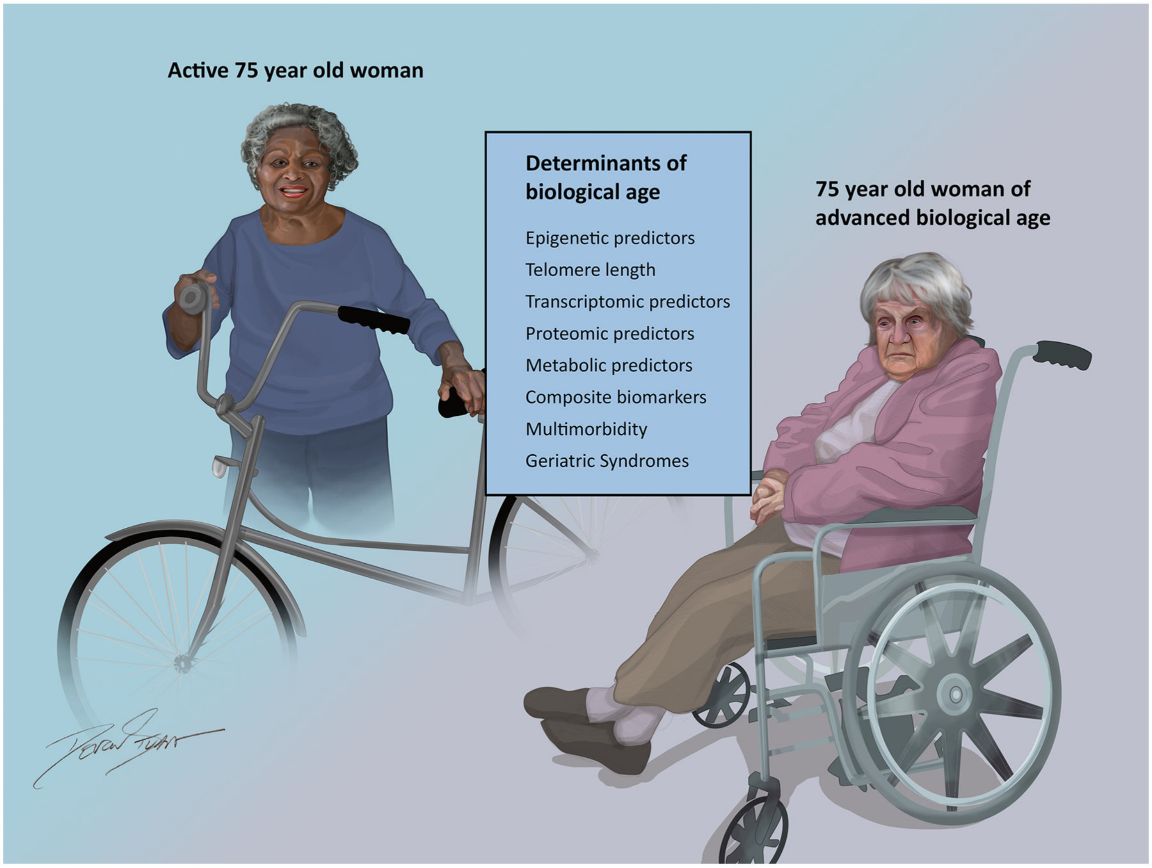

Figure 1. Contributors to the Heterogeneity of Chronological Aging.

Figure 1 highlights the array of markers and measures that contribute to the heterogeneity of “biological” aging across chronological age.

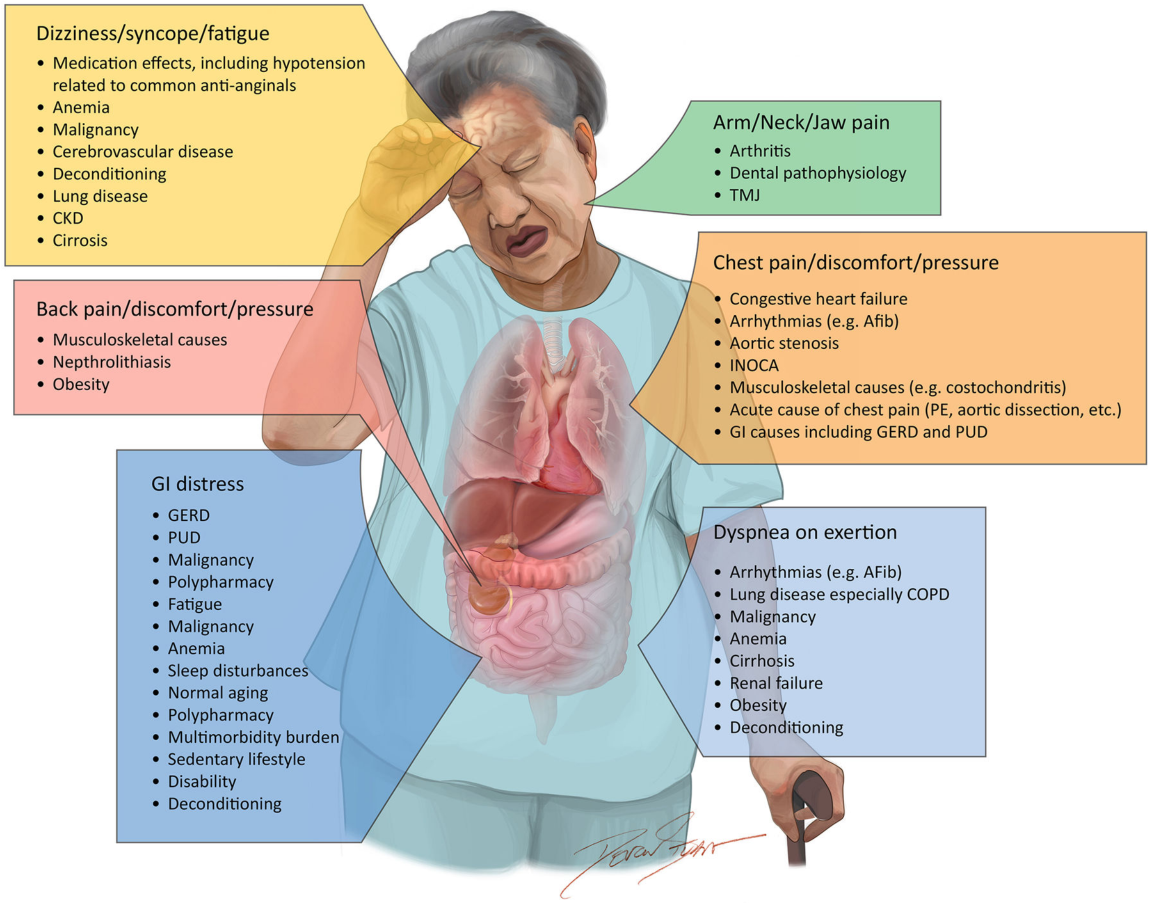

Figure 2. Interpretation of Symptoms in Older Adults with Multimorbidity.

Figure 2 presents some of the multitude of symptoms that are potentially associated with stable ischemic heart disease in older adults and examples of the potential competing conditions that can contribute to the burden of that particular symptom.

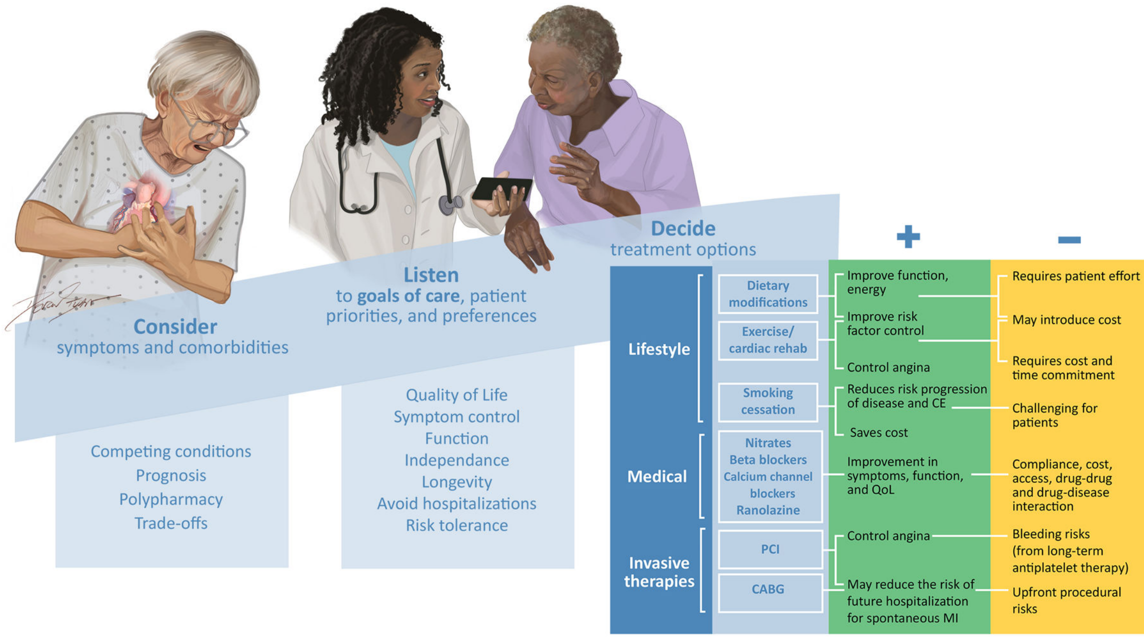

Figure 3. A Novel Framework for Approaching Treatment Decisions in Older Adults with Stable Angina.

Figure 3 presents a framework for approaching complex treatment decisions in older adults with stable angina within the context of competing conditions, individual patient priorities, preferences, and goals, as well as potential benefits, tradeoffs, and harms of the available treatments, which are listed in order of priority (lifestyle, medical, and invasive therapies).

Table 1.

Results of randomized trials of revascularization strategies in patients with stable ischemic heart disease as they relate to the older adult populations ≥75 years of age.

Trial (Author, Year)	Study Population (Sample Size)	Randomized Intervention	Average Age (Years)	Primary Endpoint	Secondary Endpoint (s)	Representation of Older Adults ≥75 Years*
ECSS (ECSSG, 1982)[59]	Men under the age of 65 with mild to moderate angina of at least 30 months with obstruction of 50% or more in at least 2 major coronary arteries (n=767)	CABG vs. Medical Therapy	Mean Age= 49.9 years (Age>53 years = 33%)	**Survival at 5 years:** CABG = 92.4% vs. Medical Therapy = 83.6% *P*<0.001	Men >53 years of age showed significant survival benefit compared with young patients	Older Adults ≥75 excluded
CASS (Passamani, 1985)[60]	Patients who were 65 years or younger with clinical and angiographic coronary disease (n=780)	CABG vs. Medical Therapy	Mean Age = 51 years	**Survival at 8 Years:** CABG = 87% vs. Medical Therapy = 84% *P* =0.14	Patients with EF<50% did have a survival advantage at 7 years with surgery (survival 84% vs. 70%, p=0.01). Those with triple vessel disease had most survival advantage with revascularization	Older Adults ≥75 excluded
RITA-2 (RITA-2 trial participants 1997)[61]	Patients with at least one significant stenosis in a major epicardial artery judged to be acceptable for medical therapy or coronary angioplasty (n=1018)	PTCA vs. Medical Therapy	Median Age = 58 years Included patients ≥70 years old (n=60)	**Death/MI at median 2.7 years follow-up:** PTCA 6.3% vs. Medical Therapy = 3.0% *P* =0.02 Difference due to one death and seven non-fatal myocardial infarctions related to randomized procedures	PTCA associated with greater symptomatic improvement, especially in those with more severe angina	Results by age ≥75 years not reported No significant interaction between treatment and age Older adults are underrepresented
VA Cooperative Study (Peduzzi, 1998)[62]	Male patients with angina pectoris (n=686)	CABG vs. Medical Therapy	51	**Survival at 7 years**: CABG = 77% Medical Therapy = 70% *P* =0.043 **Survival at 22 years:** CABG = 25% Medical Therapy = 20% *P* =0.24	MI Free Survival at 11 years: CABG = 49% Medical Therapy = 40% *P*=0.007 MI Free Survival at 22 years: CABG = 18% Medical Therapy = 11% *P*=0.003	Results by age ≥75 years not reported Older Adults are underrepresented
TIME (TIME Investigators, 2001)[5]	Patients who were 75 years or older with chronic angina with CCSC >2 and at least two antianginal drugs (n=305)	Revascularization (angioplasty) vs. Medical Therapy	Mean Age = 80 years	**QoL at 6 Months (SF-36**†): Revascularization = 11.4 Vs Medical Therapy = 3.8 *P*=0.008	Other Measures of QoL are improved with revascularization at 6 months MACE at 6 months Revascularization = 19% Vs. Medical Therapy = 49% However, no benefit with	Older Adults were represented Multimorbidity and polypharmacy were reported at baseline but effects on outcomes were not evaluated. Frailty not reported

Trial (Author, Year)	Study Population (Sample Size)	Randomized Intervention	Average Age (Years)	Primary Endpoint	Secondary Endpoint (s)	Representation of Older Adults ≥75 Years*
					revascularization at 1 year.	
DEFER (Pijls, 2007)[63]	Patients referred for elective PCI of a single angiographically significant de novo stenosis (reference diameter>2.5mm); FFR≥0.75 (n=325)	PCI vs. Medical Therapy	Mean Age = 61	**Freedom from Cardiac Event at 5 years** PCI = 73% vs Medical Therapy (Defer) = 79% *P*=0.52	Patients with FFR<0.75 had 5 times higher rate of cardiac death or AMI	Results by age ≥75 years not reported Older Adults are underrepresented
SOS (Booth, 2008)[64]	Patients with multivessel CAD (n=988)	PCI vs CABG	Mean Age ~ 61 N=395 >65 years old	Survival at 6 years: PCI = 10.9% vs CABG = 6.8% *P*=0.022	Death rate in diabetic sub-group: PCI = 17.6% vs CABG = 5.4% *However p interaction = 0.15 for treatment effect on mortality between diabetic and non-diabetic patients*	Results by age ≥75 years not reported Older Adults are underrepresented
MASS-II (Hueb, 2010)[65]	Patients with multivessel CAD and documented ischemia (n=611)	CABG vs PCI vs Medical Therapy	Mean Age = 60	**MACE at 10-years:** CABG = 33% vs PCI = 42.4% vs Medical Therapy = 59.1% *P*<0.001	Survival at 10-years: CABG = 74.9% vs PCI = 75.1% vs Medical Therapy = 69% *P*=0.089 No difference by age > vs. ≤65	Results by age ≥75 not reported Older Adults are underrepresented
FAME 2 (De Bruyne, 2014)[66]	Patients with stable coronary disease with one-, two-, or three-vessel CAD suitable for PCI (n=888)	PCI vs Medical Therapy	Mean Age = 63.5	**MACE at mean follow-up 213–214 days (trial stopped early):** PCI = 4.3% vs Medical Therapy = 12.7% *P*<0.001	Death or MI did not differ between groups, difference in MACE was driven by difference in urgent revascularization	Results by age ≥75 years not reported Older Adults are underrepresented
COURAGE (Sedlis, 2015)[58]	Patients with chronic stable angina or silent ischemia and angiographic CAD >70% stenosis (n=2,287)	PCI vs Medical Therapy	Mean Age (Extended Follow-up) = 64	**Death at 11.9 Years:** PCI = 41% vs Medical Therapy = 42% *P*=0.53	Mortality rates were similar between PCI and medical therapy groups, in both the non-VA and VA patient sub-groups. -	Results by age ≥75 years not reported Older Adults are underrepresented Age at 60 years did not modify outcome
STICH (Velazquez, 2016)[67]	Patients with CAD amenable to CABG and ejection fraction <35% (n=1,212)	CABG vs Medical Therapy	Mean Age ~60 Age 18–85 were included 308 patients >67 years old with median age in that group of 72 years.[68]	**Death at median follow-up of 9.8 months:** CABG = 58.9% vs Medical Therapy = 66.1% *P*=0.02	Secondary outcomes including death from cardiovascular causes, HF, any cause, and other MACE favored CABG.	Results by age ≥75 years not reported Older Adults are underrepresented

Trial (Author, Year)	Study Population (Sample Size)	Randomized Intervention	Average Age (Years)	Primary Endpoint	Secondary Endpoint (s)	Representation of Older Adults ≥75 Years*
BARI-2D (Ikeno, 2017)[69]	Patients with type 2 diabetes mellitus and evidence of ischemia (n=2,368)	Prompt Revascularization vs Medical Therapy	Mean Age ~ 63 Maximum age = 89.8 years.	**Death, MI or Stroke at 5 Years: Low Syntax≤22** CABG = 26.1% vs Medical Therapy = 29.9% *P*=0.41 **Moderate to High Syntax≥23** CABG = 15.3% vs Medical Therapy =30.3% *P* =0.02	Death, MI or Stroke at 5 Years: Low Syntax ≤22 PCI = 17.8% vs Medical Therapy = 19.2% *P*=0.84 Moderate to High Syntax ≥23 PCI = 35.6% vs Medical Therapy =26.5% *P* =0.12	Results by age ≥75 years not reported but results reported by age ≥70, n=514; also included health status outcomes.[70] The effect of revascularization versus medical therapy did not differ by age for death (p interaction=0.99), major cardiovascular events, angina, or health status outcomes. Older adults underrepresented
ORBITA (Al-Lamee, 2018)[6]	Patients with ≥70% single vessel stenosis. (n=230)	PCI vs Placebo Procedure	Mean Age = 66	**Exercise Time** did not improve with PCI compared with Placebo Procedure (Difference in increment between groups = 16.6 seconds, *P*=0.200)	No improvement in CCSC, Seattle Angina, or EQ-5D-5L Questionnaire with PCI	Results by age ≥75 years not reported Older Adults are underrepresented
FREEDOM (Farkouh, 2019)[71]	Patients with diabetes and multivessel CAD with diameter stenosis ≥70% in 2 or more major epicardial vessels involving with 2 separate coronary territories (n=1,900)	CABG vs PCI	Mean Age ~ 63	**All-cause mortality at median follow-up 7.5 Years:** CABG = 18.3% vs PCI-DES = 24.3% *P*=0.01	Younger patients (≤63.3 years) derived preferential benefit from CABG compared with older patients (>63.3 years), *P* for interaction = 0.001	Results by age ≥75 years not reported Older Adults are underrepresented
ISCHEMIA (Maron, 2020)[7]	Patients with stable coronary disease and moderate or severe ischemia (n=5,179)‡	Invasive vs Conservative Strategy	Mean Age = 64	**MACE at median follow-up of 3.2 Years**: Hazard Ratio 0.93 (95%CI 0.80 to 1.08) for invasive vs. conservative strategy. **Estimated cumulative event rate at 6 months:** Invasive Strategy =5.3% vs Conservative Strategy = 3.4% (difference, 1.9 percentage points; 95% CI, 0.8 to 3.0) **Estimated cumulative event rate at 5 years:** Invasive Strategy =16.4% vs Conservative Strategy = 18.2% (difference, −1.8	Modest improvement in angina-related health status with invasive strategy, driven by greater benefit in those with more symptomatic patients and those with moderate to severe ischemia.[72]	Results by age ≥75 years not yet reported Older Adults are underrepresented

Trial (Author, Year)	Study Population (Sample Size)	Randomized Intervention	Average Age (Years)	Primary Endpoint	Secondary Endpoint (s)	Representation of Older Adults ≥75 Years*
				percentage points; 95% CI, −4.7 to 1.0)		
ISCHEMIA-CKD (Bangalore, 2020)[57]	Patients with advanced kidney disease and moderate or severe ischemia (n=777)	Invasive vs Conservative Strategy	Median Age = 63	Death from any cause or MI at 3 Years: Invasive Strategy = 36.4% vs Conservative Strategy = 36.7% *P*=0.95	Death from any cause, MI, Hospitalization for Angina or Heart Failure, or Resuscitated Cardiac Arrest at 3 Years Invasive Strategy = 38.5% vs Conservative Strategy = 39.7%	Results by age ≥75 years not reported Older Adults are underrepresented

*Representation of Older Adults ≥75 years refers refer to both 1) the inclusion of individuals with chronologic age ≥75 years, as well as 2) the underrepresentation of geriatric participants including those with geriatric syndromes and reporting on those conditions

†SRF-36 score 0 to 100 with higher scores indicating more favorable status.

‡Patients were excluded if they had eGFR<30, a recent acute coronary syndrome, unprotected left main of at least 50%, systolic dysfunction of less than 35, New York Heart Association class III or IV heart failure, and unstable angina.

Abbreviation: CCSC: Canadian Cardiovascular Society Class; QoL = Quality of Life; MACE = major adverse cardiovascular events; PCI = percutaneous coronary intervention; FFR = Fractional Flow Reserve; AMI = Acute Myocardial Infarction; CAD = coronary artery disease; MI = Myocardial Infarction; DES = Drug Eluting Stent; PTCA = Percutaneous transluminal coronary angioplasty.