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COP: Cholesterol

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       Healthcare in the United States is costly, particularly for the most prevalent diseases and disorders that are risk factors for developing preventable diseases. Heart disease is the leading cause of death of all adults in the US, with death rates of 168.2 per 100,000 population.[1] This ends up costing a total of $241 billion in annual treatment costs for an estimated 100.2 million people.[2,3] High cholesterol is a top modifiable risk factor for heart disease, costing $18.5 billion in annual treatment costs including $4.02 billion for the most common statins alone.[4] Out of an estimated 94 million people with high cholesterol, only 45.9 million are receiving treatment.[3,5,6] Healthy People 2030, a series of public health initiatives put forth by the US Department of Health and Human Services, has set goals to reduce high cholesterol morbidity and heart disease mortality.[7-9] Middle aged adults are the age group most impacted, demonstrating a need to increase focused patient education on high cholesterol prevention and management to reduce heart disease death.

       High cholesterol is a health issue that impacting the health of adults in the United States. According to Healthy People 2030, mean total cholesterol levels are high in the population at 190.9 mg/dL, yet only 44.9% of adults with high cholesterol are receiving treatment.[8,9] High cholesterol levels are a major risk factor in developing cardiovascular disease, which is the leading cause of death in adults.[10] Middle aged adults between ages 45 and 64 suffer the highest prevalence and levels of hypercholesterolemia, and prevalence of heart disease.[11,12] Deaths from coronary heart disease in adults are 91.8 per 100,000 population.[7] In order to improve the health of the American population, it is important middle-aged adults are educated of the risks having

high cholesterol poses on their heart health, and the treatment options available with dietary pattern modification and statin use.[10,13]

To understand the detrimental effects high cholesterol poses to the health of the middle-aged US population, first we must understand the pathophysiology behind lipid disorders, high cholesterol as a risk factor for heart disease, and the resulting mortality. Some terms associated with these disorders are dyslipidemia which refers to any disorder of lipid levels, hyperlipidemia which is generally elevated lipid levels, and hypercholesterolemia which specifically refers to elevated total cholesterol.[14-16] Cholesterol is a lipid compound that is the precursor molecule to all steroids within the body such as hormones, corticosteroids, and bile acids. The molecule has a characteristic structure with a core of hydrocarbon rings and hydrocarbon tail.[14] Roughly 50% of cholesterol in the body is synthesized, with about 10% occurring in the liver and intestine. The remainder is absorbed from dietary sources in the average diet, though foods high in fats lead to an excess of absorbed cholesterol.[15,16]

Focusing on dietary cholesterol, these hydrophobic molecules must be bound to apoproteins (apolipoproteins) in order to be transported through the circulatory system.[15,16] These lipoproteins come in multiple forms, with the most applicable to clinical use being low-density lipoproteins (LDL) and high-density lipoproteins (HDL). The total serum cholesterol level counts both LDL and HDL as well as other lipid components.[16] The density refers to how much lipid is contained in the molecule, with lipid being less dense than water (blood). LDL cholesterol is less dense and therefore is very lipid rich, saturated in cholesterol. Conversely, HDL cholesterol is denser meaning it is unsaturated and low in cholesterol.[16] These transport molecules serve to take cholesterol from the liver out to cells via LDL, and return excess cholesterol back to the liver via HDL. Normally, excess cholesterol is excreted into the GI tract

as bile salts and is eliminated in stool.[15,16] Clinically, total cholesterol levels can be measured in a serum sample. After a process to separate certain apolipoproteins, the HDL cholesterol can be measured. Then LDL cholesterol is calculated using an equation called the Friedewald formula.[16] This is important because dysfunction anywhere in this complex system can result in high levels of cholesterol circulating and/or deposited in tissues, including arteries and the heart. LDL cholesterol in particular has been shown to be highly atherogenic, meaning more contributory to plaque deposition in arteries and leading to atherosclerosis, than HDL cholesterol which is not atherogenic.[13] Lowering LDL levels is shown to positively improve overall health and reduce ASCVD risk, making it a specific target for treatments.[10,13]

Middle aged adults in the US have some of the highest and now increasing rates of heart disease deaths, and highest prevalence of major risk factors like hypercholesterolemia. Data from the National Center for Health Statistics (NCHS) revealed from 2015 to 2018, that 11.4% of all adults aged 20+ in the US had high total cholesterol levels ≥240 mg/dL.[17] Higher total cholesterol is known to be a major risk factor for developing atherosclerotic cardiovascular disease (ASCVD), resulting in deaths from myocardial infarctions and strokes.[10,13] Middle-aged may not be as aware as older adults are of the risk high cholesterol poses to their health, and this is reflected in the prevalence differences between age groups. Adults aged 40-59 had the highest prevalence of 15.7%, compared to adults aged 60+ with prevalence of only 11.4%.[17] In CDC data from 2015-2018, the mean total cholesterol level for all adults aged 20+ in the US was 191 mg/dL.[11] This was further defined by age groups and self-identified sex. The highest for males was ages 45-54 with a mean total cholesterol of 200 mg/dL. The highest for females was a little later in ages 55-64 with a mean of 210 mg/dL. Notably, females aged 45-54 were close with a mean of 204 mg/dL.[11] According to the 2018 Cholesterol Clinical Practice Guidelines, a total

cholesterol level target of ≤150 mg/dL was associated with lower risk of ASCVD.[13] For middle-aged adults with hypercholesterolemia, total levels in the 200s are clearly significantly higher than the optimal levels, and pose a health risk.

Similarly, the level of high-density lipoprotein (HDL) cholesterol is another risk factor, though not independently. Lower HDL levels are associated with higher LDL levels, which is linked to higher ASCVD risk and resulting mortality.[10] Data from the NCHS between 2015 and 2018 showed that the prevalence of HDL levels <40 mg/dL amongst all adults aged 20+ was 17.2%.[17] Again, middle-aged adults had the highest prevalence of low HDL levels amongst all other age groups, with ages 40-59 at 18.5% compared to ages 60+ only at 14.6%.[17] Low HDL levels correlate with high total cholesterol levels and thus high LDL levels, which directly contribute to the accumulation of atherosclerotic plaques and increased risk of ASCVD. More focus is required on the middle-aged population who are suffering the greatest disease burden for hypercholesterolemia. These adults aged 45-64 suffer the greatest prevalence and have the highest average total cholesterol levels compared to all other age groups. More work needs to be done to help these patients. If we can manage modifiable risk factors like total cholesterol levels earlier in life, then we can reduce the risk patients will develop ASCVD later in life and suffer negative health outcomes. Patient education targeted at middle aged adults and even young adults is required to make progress toward improving the population's heart health.

Heart disease is a very broad term that includes structural and valvular disorders, arrhythmias, heart failure, cardiovascular diseases, and more. Cardiovascular disease (CVD) refers a more specifically to diseases affecting the heart, brain, and vasculature including coronary heart disease (CHD) that affects the coronary arteries feeding the heart. Atherosclerotic cardiovascular disease (ASCVD) is CVD that is caused by cholesterol plaque buildup in arteries

in a process called atherosclerosis.[18] Atherosclerosis is the hardening of arteries due to factors like old age and disorders like hypercholesterolemia, that results in decreased arterial wall compliance and function. Major risk factors for developing CHD also include old age, dyslipidemias, hypertension, and cigarette use.[19] The combination of these risk factors leads to functional changes of the vascular lining, allowing high levels of circulating LDL cholesterol to begin to accumulate within the intima of coronary arteries as plaque.[19,20] Over time this plaque grows in size and reduces the diameter of the vascular lumen, restricting blood flow and causing oxygen demand and supply mismatch to cardiac tissue.[20] In cases of acute myocardial infarction (MI), the plaque dome has ruptured and precipitates platelet aggregation and clotting due to endothelial damage. Complete occlusion of the coronary artery during an acute MI result in myocardial ischemia and potentially significant cardiac dysfunction.[19,20]

According to the CDC and data from the National Center for Health Statistics, heart disease is the leading cause of deaths in adults. In 2019, heart disease accounted for 23.1% of all deaths, numbering 659,041 deaths.[21] By age, heart disease accounted for 25.1% of deaths in adults aged 65+ and 28.7% of deaths in adults aged 85+. In adults aged 45-64, heart disease was the second most common cause of death, accounting for 20.9% of deaths.[21] In 2020, the rate of deaths from heart disease increased by 4.1%.[1] Middle aged adults are the most at risk for developing CVD and have the highest prevalence of hypercholesterolemia. This results in high prevalence of heart disease in older age, accounting for the most common cause of death in adults aged 65 and older. Healthy People 2030 has set a goal of 71.1 per 100,000 deaths, yet we currently stand worse at 91.8 per 100,000.[7] According to the AHA, old age is the number one risk factor for developing CVD, which we have no interventions for.[10] We can, however,

intervene with reduction of modifiable risk factors like cholesterol levels to effectively lower individual risk for ASCVD.

Hypercholesterolemia and the often-associated cardiovascular disease are treated both from a primary prevention and secondary prevention standpoint. The key in both is decreasing the extent of hypercholesterolemia with targeted therapies and lifestyle modification to reduce levels of total and LDL cholesterol.[10,13] Diet modification focusing on decreasing or replacing saturated fat intake, and increasing vegetable and fruit intake is effective in reducing the risk of high cholesterol leading to CVD.[22] In addition, effective pharmacologic therapies for lowering cholesterol levels include the drug class HMG-CoA reductase inhibitors, or "statins", that are shown to reduce CVD risk and all-cause mortality.[23,24] Initial primary prevention choice for middle-aged adults aged 40-75 depends on their calculated 10-year ASCVD risk score, and will guide how aggressively to treat the hypercholesterolemia and other risk factors.[10,13,24] For individuals who score 5% or lower are generally recommended to start with lifestyle modification including changing dietary patterns, and only beginning at 5-7.5% do we use shared decision making to decide on statin therapy in addition to diet and lifestyle. Individuals with risks 7.5-20% and especially >20% should initiate statin therapy with the highest risk immediately starting on high intensity statins.[10,13,24] The presence of any comorbid factors like diabetes, chronic kidney disease, metabolic syndrome, or other risk enhancers further adjusts when to begin aggressive prevention measures.

Lifestyle modification beginning with changing diet patterns is a safe and effective primary preventative measure all patients with high cholesterol and risk for CVD should do. The Dietary Guidelines for Americans (DGA) 2020-2025 is a set of recommendations from the US Department of Agriculture and the US Department of Health and Human Services aimed at

improving the diet and nutrition of the population to prevent disease.[25] The Health Eating Index-2015 (HEI) used in the DGA is a measure of how well current daily dietary intake matches the recommended amounts. Middle-aged adults 31-59 scored 59 out of 100 which indicates a significant mismatch.[25] Adults are currently ingesting barely half the recommended daily amounts of fruits and vegetables, while being far over the daily limit for saturated fats. The daily limit for saturated fat is 10% of total daily energy intake, and currently 76% of males and 71% of females are over the limit.[25] The American Heart Association (AHA) recommends reducing saturated fat intake and substituting with less atherogenic poly-unsaturated fats, increasing the intake of fruits and vegetables, and substituting plant-based sources of protein over animal protein.[26]

In a 2013 Cochrane review of diet studies, increasing fruit and vegetable intake by 1.18 servings/day each led to statistically significant reductions in total serum cholesterol level by 0.15 mmol/L (5.8 mg/dL), and LDL cholesterol by 0.16 mmol/L (6.19 mg/dL) after at least 12 months.[27] This increase of servings would approximately bring daily intake into DGA recommended levels, and effectively reduces total and LDL cholesterol levels which is known to reduce ASCVD risk. Furthermore, a 2020 Cochrane review found that reducing dietary saturated fat intake to <10% through a variety of dietary interventions led to not only reduced cholesterol levels, but also statistically significant reduction in CVD events.[22] This resulted in a 21% reduction in combined cardiovascular disease events with a number needed to benefit of 56 in primary prevention studies, and a 17% reduction in coronary heart disease events, but no effect on CVD or CHD mortality.[22] Total cholesterol and LDL levels were reduced by 0.24 mmol/L (9.28 mg/dL) and 0.19 mmol/L (7.35 mg/dL) respectively, which supports the findings of the 2013 Cochrane review.[22,27] While these interventions may not show evidence of reducing end

mortality from CVD, there is evidence supporting their efficacy in reducing risk, thereby reducing prevalence of disease. Patients at risk of developing ASCVD due to high cholesterol should be supported to make these dietary changes in order to benefit from these evidence-based interventions.

Patient education centered on education and guidance through multiple follow ups and high intensity counseling is shown to have better results on lowering cholesterol levels and long-term adherence to diet than one time instruction. Longer term dietary counseling that focuses on promoting healthy eating habits and making changes in line with the DGA 2020-2025 recommendations is more effective than a single education event or a patient by themselves. A recent 2021 meta-analysis of dietary counseling published in Nutrients found that dietician led high intensity counseling lowered cholesterol levels in middle aged adults.[28,29] High intensity counseling consisted of 6 sessions with a dietician of at least 30 minutes duration, over a period of 6 months in some studies. There were statistically significant reductions in total cholesterol by 0.31 mmol/L (11.99 mg/dL), and LDL cholesterol by 0.39 mmol/L (15.08 mg/dL) when compared to a physician led group consisting of a single meeting.[28] It is important to provide ongoing guidance and follow up with patients as this allows better adherence to the dietary plan and the ability to monitor the effects of treatment. Patients can have more education and assistance from the dietician, who is the content expert for implementing a dietary plan, instead of relying on information learned from inconsistent visits with a physician. This is not to say a trained clinician with experience in dietary modification would not be able to be as effective as a dietician was found to be in these studies. The focus should be on providing the patient with the right education and have ongoing guidance. This will amplify the benefits of making dietary changes, and further decrease ASCVD risk.

For patients initially at high ASCVD risk, or who have not been able to achieve lowered cholesterol levels on lifestyle modification alone, medication management with statins is recommended and shown to effectively lower total cholesterol and specifically LDL cholesterol.[10,13] Patients with intermediate to high risk, meaning ASCVD 10-year scores of 7.5-20% and higher, immediate initiation of statin therapy is recommended with a moderate to high intensity statin.[10] The US Preventive Services Task Force (USPSTF) released updated 2022 recommendations for statin use in the prevention of cardiovascular disease.[24] For adults aged 40-75 with at least 1 CVD risk factor and 10-year ASCVD risk score of 10% or more, initiation of statin use was recommended.[24] For adults in the same age range and risk factors but with a 10-year ASCVD risk score less than 10%, shared decision making with the patient and clinician was recommended to decide whether to start statins or not.[24] The USPSTF found that statin use in patients aged 52-66 had statistically significant reduction in all-cause mortality and specifically reduced CVD events, however no reduction in CVD mortality.[24] A 2013 Cochrane review found that statin use for primary prevention had a statistically significant reduction in all-cause mortality, coronary heart disease events, and cardiovascular disease events. They found that in high-risk patients of mean age 57, statins reduced the risk of a first time CVD event where, if not on statins for 5 years, 18 out of 1000 would have had a major CVD event.[23] Statins are proven effective in reducing LDL levels by differing percentage depending on the intensity of statin used. The initial level recommended of moderate intensity statins typically reduce LDL cholesterol levels between 30-50%, and high intensity statins recommended for high-risk patients can reduce LDL by upwards of 50%.[10] While these reductions in LDL does not lead to a reduction in mortality, it does decrease ASCVD risk and as the Cochrane review highlighted, a reduction in CHD events.[23] Patients should be counselled on the need for starting a statin based

on their personal risk factors, and the benefits to reducing their LDL cholesterol and CHD risk. It is equally important to ensure they continue taking their statin to keep their cholesterol levels controlled.

Heart disease is the leading cause of death for Americans, and middle-aged adults have the highest prevalence of high cholesterol which is a major risk factor for atherosclerotic cardiovascular disease. Effective primary prevention for high cholesterol based on stratified personal risk begins with dietary modification per the DGA recommendations, and close guidance with a trained clinician. Additional medication therapy with statins to further lower LDL cholesterol can then be started if diet is inadequate. These management guidelines from the AHA and USPSTF are shown to reduce CVD risk and first-time major events for high-risk individuals. Clinicians must work with their patients to counsel them about their individual risk factors and how to start and adhere to a management plan incorporating all these guidelines. These benefits are not reserved only for cholesterol and CVD. There are positive health benefits for hypertension, diabetes, obesity, and many other chronic health diseases. In this way, we can improve the health of all Americans and promote longer healthier lives.

The approach to educating middle-aged adults on cholesterol and heart disease is raising awareness with the goal of initiating a discussion with their own primary care provider. This can be accomplished through a presentation with visual aid such as a PowerPoint or poster. In this modern age, virtual presentations can be used to access a wider audience without relying on the need to travel to a specific location. Virtual presentations also allow for the possibility of asynchronous viewing, though this will remove the ability for audience members to ask live questions. However, in some settings, a traditional in person presentation may be better for communities that may not have access to electronic devices or reliable internet. A short

presentation arranged with background information, the current state of heart disease and cholesterol levels in the middle-aged population, an overview of current evidence-based management strategies, and closing thoughts. Immediately following, a short question and answer session can help address specific audience member questions, though no answers with constitute individual medical advice. Additionally, the community partner can help with further local resources and information being made available during the presentation. Some of the more impactful resources would be for dietary guidance, local food programs, health centers and screening events, and any other pertinent local programs. All of this combined will hopefully prompt those in attendance to reflect on their personal health situation and lead to further follow up with a healthcare provider. This will all be the first step in achieving the Healthy People 2030 goals of lower heart disease mortality, lower total cholesterol, and greater treatment.

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26.   Carson JAS, Lichtenstein AH, Anderson CAM, et al. Dietary Cholesterol and Cardiovascular Risk: A Science Advisory From the American Heart Association. *Circulation*. Jan 21 2020;141(3):e39-e53. doi:10.1161/cir.0000000000000743
>   Journal article investigating the current management guidelines for high cholesterol and CVD risk including the current average diet, related cholesterol levels, and interventions to improve health for individuals eating a Standard American Diet. Limitations could include omissions of diets other than the SAD which may not allow the information to apply to a diverse population.

27.   Rees K, Dyakova M, Wilson N, Ward K, Thorogood M, Brunner E. Dietary advice for reducing cardiovascular risk. *Cochrane Database Syst Rev*. Dec 6 2013;(12):Cd002128. doi:10.1002/14651858.CD002128.pub5
>   Cochrane review of using dietary modification to increase vegetables and fruits for cardiovascular disease risk reduction. It included 44 RCTs that included around 18,000 participants. The authors compiled the data and carried out statistical analysis and reported the results with statistically significant findings. The authors also discussed the data in order to report the evidence-based results. Some limitations include about half (29) of the studies were conducted in the US, meaning the remaining involved healthcare systems and participants that may differ from the US. Not all methods and interventions may be transferrable to the US population. Additionally the review from 2013 may not fully reflect more up to date stuides and methods, however a more recent review was not found.

28.   Low JHM, Toh DWK, Ng MTT, Fam J, Kua EH, Kim JE. A Systematic Review and Meta-Analysis of the Impact of Different Intensity of Dietary Counselling on Cardiometabolic Health in Middle-Aged and Older Adults. *Nutrients*. Aug 25 2021;13(9)doi:10.3390/nu13092936
>   Journal article with meta-analysis of 22 studies of structured dietary counseling at differing levels of intensity and determining the effectiveness of improving high cholesterol levels. The statistical analysis resulted in statistically significant findings for counseling at three intensity levels. Some limitations include variation in study length and adherence of participants to diet interventions.

29.   Sialvera TE, Papadopoulou A, Efstathiou SP, et al. Structured advice provided by a dietitian increases adherence of consumers to diet and lifestyle changes and lowers blood low-density lipoprotein (LDL)-cholesterol: the Increasing Adherence of Consumers to Diet &

Lifestyle Changes to Lower (LDL) Cholesterol (ACT) randomised controlled trial. *J Hum Nutr Diet*. Apr 2018;31(2):197-208. doi:10.1111/jhn.12508

> Journal article of a study from Greece investigating the effectiveness of dietary counseling performed by a dietician vs physician and the effects on LDL cholesterol levels. Specifically named trained clinicians like dietitians as an effective intervention for treatment adherence. Limitations include a small study of one particular population with a potential difference in baseline diet and healthcare system.