Quarterly Medication Review Deprescribing Focus

LONG TERM CARE

ASA and Statins for Primary Prevention

January to March 2023

Background

- As the health status and goals of care for an individual in a LTC setting change, the use of medications for primary prevention of cardiovascular (CV) disease should be reviewed
- Some residents may be using ASA and/or lipid lowering medications (e.g., statins) who do not have a history of cardiovascular or cerebrovascular disease (i.e. primary prevention).

For the quarterly medication reviews from January to March 2023, reassess all residents on ASA or statins. If using for primary prevention of cardiovascular (CV) disease, consider deprescribing.

For all residents on ASA:

- Determine the indication for low dose ASA
- Based on current evidence, consider discontinuing ASA if being used solely for primary prevention of CV disease

For all residents on statins:

- Determine whether the statin is being used for primary or secondary prevention of CV disease
- If being used for primary prevention, consider the benefits and harms of ongoing treatment:
  - ◊ Resident's cardiovascular risk
  - ◊ Resident's goal of care
  - ◊ Adverse events (see Table 1 - Statin Adverse Events on page 5)
  - ◊ Drug interactions
  - ◊ Pill burden/medication pass time; polypharmacy
  - ◊ Goals of care
- Consider discontinuing or decreasing the dose of statin being used for primary prevention of CV disease
- Assess if any of the other medications the resident is taking interacts with statins. Reducing the dose or stopping a statin may necessitate dose adjustments or monitoring of other medications the resident is taking

QMR Contents:

Attachments included with QMR:

- RxFiles: ASA (Aspirin) for Primary Prevention of Cardiovascular Disease
- Price Comparison of Commonly Prescribed Antihypertensive Medications in Manitoba 2022 → Lipid lowering agents

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ASA for Primary Prevention in LTC Residents

Guideline Recommendations

- Hypertension Canada no longer recommends the use of ASA for primary prevention of cardiovascular disease in adults with hypertension. There is little evidence of overall benefit but increased risk of major bleeding[1]
- The Canadian Stroke Best Practice Recommendations and Thrombosis Canada do not recommend low dose ASA for primary prevention of a first vascular event[2]
- The Beers Criteria recommends cautious use of ASA in those 70 years and older due to a lack of evidence for benefits and risks in this population[3]
- Diabetes Canada's 2020 clinical practice guidelines state that "ASA should not routinely be used for primary prevention of CVD in people with diabetes"[27]
- 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease[28] indicates ASA 75-100mg daily should not be administered on a routine basis for the primary prevention of atherosclerotic CVD among adults 70 years of age and older

Evidence for ASA in Primary Prevention

- Three large randomized controlled trials from 2018 assessed the benefits and harms of ASA for primary prevention in different populations[4]
    - Aspirin in Reducing Events in the Elderly trial (ASPREE)[5] included patients 70 years and older living in the community
        - No statistically significant positive association of ASA use with either CVD mortality or all-cause mortality
        - Significant increase in intracranial and extracranial hemorrhage observed. HR 1.38 (95% CI 1.18-1.62) ARI 1.03%, NNH 100
        - Conclusion: Avoid ASA for primary prevention in individuals who are 70 years of age and older
    - A Study of Cardiovascular Events iN Diabetes trial (ASCEND)[6] included patients 40 years of age and older with diabetes and without CVD
        - The primary endpoint favoured ASA use but this was after the primary endpoint was expanded, the sample size increased, and the duration of follow-up extended; 8.5 % vs 9.6%, RR 0.88 (95% CI 0.79-0.97), ARR 1.1%, NNT 91
        - Increased risk of major bleeding: 4.1 vs 3.2%, RR 1.29 (95% CI 1.09-1.52), ARI 0.9%, NNH 112
        - The absolute benefits from avoiding serious cardiovascular events were largely counterbalanced by the increased risk of bleeding; 91 people would need to be treated with low-dose ASA for 7.4 years in order to prevent one additional MI, stroke/TIA or vascular death (NNT), and 112 would need to be treated to cause one additional major bleed (NNH)
        - Taking low-dose ASA for 7.4 years can lower the risk of MI, stroke, TIA or vascular death by 12% (RRR), but increases the risk of major bleeding by 29% (RRI)
    - The Aspirin to Reduce Risk of Initial Vascular Events trial (ARRIVE)[7] included patients with low to moderate cardiovascular risk
        - No significant difference in composite CV outcome (CV death, MI, unstable angina, stroke, TIA)
        - Increased risk of GI bleed – HR 2.11 (95% CI 1.36-3.28), ARI 0.51%, NNH 196
    - A 2019 systematic review and meta-analysis of data from 13 trials comprising 164,225 individuals without cardiovascular disease to evaluate the association between aspirin use and cardiovascular and bleeding events found a lower risk of cardiovascular events but a higher risk of major bleeding[9]

ASA Deprescribing Recommendations

- As the benefits of ASA for primary CV prevention may be nonsignificant and/or be largely counterbalanced by adverse effects such as intracranial bleeding and gastrointestinal bleeding, it is recommended that low dose ASA be stopped if being used for primary CV prevention solely

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Statins for Primary Prevention in LTC Residents

- Recommendations for use of statins in primary prevention are not as well established for those over 75 years old as compared to younger patients
- Cardiovascular risk assessment tools (e.g. Framingham Risk Score) are not validated for those over 75 years old and therefore use of these tools to assess cardiovascular risk is not recommended in this population[11,12,13]
- Lipid levels may not be correlated with cardiovascular risk and mortality in older adults and the beneficial effect of statins therefore may be independent of total cholesterol level[12,14]

Guideline Recommendations

- The 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults states that "… accumulating evidence suggests continued benefits of lipid-lowering for primary prevention in older adults (older than 75 years)."[11]
    - ♦ However, the meta-analysis that showed benefits of lowering LDL cholesterol in those 75 years and older noted that there is limited evidence for benefits of lipid lowering for CV risk reduction for **primary prevention** in older patients, as **less than a quarter of major vascular events were in primary prevention patients,** and an open-label trial was heavily weighed in the analysis[15]
- Canadian Family Physician Clinical Practice Guidelines: Simplified Lipid Guidelines Prevention and Management of Cardiovascular Disease in Primary Care[13] : For patients older than 75 years old, routine testing of lipid levels, estimating lipid CVD risk, and prescribing statins is discouraged (moderate-level evidence)
- 2018 ACC/AHA Guideline on the Management of Blood Cholesterol[16]: In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy

Evidence for Statins in Primary Prevention

Benefits

- 2017 meta-analysis of JUPITER and HOPE-3 Trials[17] Rosuvastatin for primary prevention in the subgroup of patients over 70 years old resulted in a 26% relative risk reduction for the composite endpoint of nonfatal MI, nonfatal stroke, and cardiovascular death (HR 0.74 95% CI 0.61-0.91)
    - ◊ Authors noted that there was a modest number of participants 80 years and older and although benefit is still likely in this older age group, benefits should be weighed against other patent-specific factors
- Meta-analysis of statin use in primary prevention[18] — Statins compared with placebo significantly reduced the risk of MI and stroke, but not the risk of all-cause mortality or cardiovascular death
    - ◊ Mean age of 73 and mean follow up of 3.5 years
    - ◊ MI: RR 0.606 (95% CI 0.434-0.847), NNT = 84 over ~3.5 years; Stroke: RR 0.762 (95% CI 0.626-0.926), NNT = 143 over ~3.5 years

Lack of benefits

- PROSPER randomized controlled trial[19] — Effect of pravastatin on reducing the primary composite endpoint of coronary death, non-fatal MI, and fatal or non-fatal stroke in those age 70-82
    - ◊ In the subgroup of patients with no previous vascular disease, results were not significant – HR 0.94 (95% CI 0.77-1.15)
- Retrospective cohort study[20] — Effect of statins in primary prevention in reducing the incidence of atherosclerotic cardiovascular disease (CVD) and all-cause mortality in old (75-84 years) and very old (85 years and older) patients with or without diabetes
    - ◊ No reduction in atherosclerotic CVD or all-cause mortality in patients without diabetes or those with diabetes 85 years and older
    - ◊ Significant reduction in atherosclerotic CVD (HR 0.76, 95% CI 0.65-0.89) and all-cause mortality (HR 0.84, 95% CI 0.75-0.94) in those with diabetes aged 75-84 years

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Evidence for Deprescribing Statins

- Randomized clinical trial[21] — Assessed the safety and benefits of statin discontinuation in those with advanced, life-limiting illness. Adults with estimated life expectancy of 1 month to 1 year and who had used statins for 3 months or more for primary or secondary prevention and had recent deterioration in functional status and no recent active cardiovascular disease were randomized to either discontinue or continue their statin[21]
    - ◊ No significant difference in death within 60 days between the two groups. Noninferiority end point was not achieved, as the upper limit of the 90% confidence interval for difference in proportion of participants who died within 60 days was above 5% (10.5%).
    - ◊ There were few cardiovascular events in both groups and improved quality of life (QOL) in the statin discontinuation group (determined by McGill QOL score—mean score 7.11 in discontinuation group vs 6.85 in those continuing statins, P=0.04)

Statin Dose Reduction *(for specific vulnerable residents who are at increased risk of statin-related adverse events)*

- A cohort study using population-based administrative data included 21,808 residents in long-term care facilities who were 76 years of age and older taking intensive dose statins (atorvastatin 40 mg or higher, rosuvastatin 20 mg or higher, simvastatin 80 mg or higher) to moderate dose statins (atorvastatin less than 40mg, rosuvastatin less than 20 mg, simvastatin less than 80 mg, any pravastatin, any lovastatin, any fluvastatin)
    - ◊ 1-year cumulative incidence of admission to hospital for cardiovascular events was 11.41% in residents taking high intensive-dose statins and 11.45% in those taking moderate doses, with a risk difference in outcomes of −0.04% (95% CI −1.34% to 1.26%)
    - ◊ One-year survival for matched residents taking high intensive and moderate dose statins was 74.37% and 73.56%, respectively
    - ◊ The risk difference in 1-year survival between the treatment groups was not significant (0.81%, 95% confidence interval [CI] −0.99% to 2.61%)
    - ◊ No significant association between 1-year survival and receiving high intensive-dose versus moderate-dose statins (hazard ratio [HR] 0.97, 95% CI 0.90 to 1.05) using Cox proportional hazard modelling

Factors that Support Deprescribing Statins

- **Goals of care:** May shift from prolonging life to improving quality of life; may no longer value preventative therapies
- **Adverse events:**[12] See Table 1. Statin Adverse Events below
    - ◊ Higher risk of adverse events in older adults due to increased exposure as a result of decreased body size and reduced muscle mass
    - ◊ Adverse effects are more problematic in older patients, especially those with metabolic disturbances, kidney or liver compromise, or polypharmacy
    - ◊ The risks of statin associated side effects may be heightened by increased statin doses[29]

Table 1. Statin Adverse Events[12,25]

Gastrointestinal	Diarrhea, constipation, nausea, dyspepsia
Muscle symptoms	Myalgia (5-10%), myositis (rare, 0.1%), rhabdomyolysis (rare, 0.01%) Higher risk and greater impact due to age-related factors such as decreased muscle mass
Hepatic dysfunction	Increase in liver enzymes (ALT greater than 3 times the upper limit of normal), dose-dependent
Acute kidney injury	Associated with high potency statins, stronger association within 4 months of starting therapy
Cognitive impairment	Some reports of reversible cognitive impairment, although other evidence (including a 2021 systematic review)[26] show no negative effect of statins on cognitive function
Diabetes	Increased risk of developing diabetes, with a higher risk for those on higher intensity statins Could be due to effects on glucose metabolism

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Factors that Support Deprescribing Statins continued...

- **Drug interactions:**[22,23] There are several drug interactions involving lovastatin, simvastatin, atorvastatin. Fewer interactions involve pravastatin, rosuvastatin, and fluvastatin
    - ◊ Examples of medications that interact with either some or all statins (list is not exhaustive): cyclosporine, warfarin, phenytoin, rifampin, clarithromycin, verapamil, diltiazem, azole antifungals, colchicine
    - ◊ Consequences of drug interactions vary depending on the statin and the interacting medication[23].
        - * Interactions that increase concentration of statins which can increase the risk of statin toxicity (e.g., fluconazole)
        - * Interactions where statins can increase or decrease the concentrations of other medications. For example, all statins except for atorvastatin may increase anticoagulant effects of warfarin, which requires increased monitoring and possible dose adjustments if a statin is started, discontinued, or dose has changed
- **Pill burden/time for medication pass**
- **Polypharmacy**
- **Cost:** Refer to *Lipid Lowering Agents Price Comparison* (attached)

Statin Deprescribing Recommendations[24]

- Consider the risks versus benefits of statin treatment based on resident-specific factors. Refer to Figure 1. Benefits and Harms of Statins below to help assess benefit and risk of statin treatment for each resident
    - ◊ If benefit of treatment for primary CV prevention is deemed to still outweigh the risks of statin treatment (e.g. resident is under 85 years of age and has diabetes) consider decreasing the statin from a high intensity statin dose to moderate intensity one to reduce the risk of adverse effects. See Table 2. Statin Intensity Dosage Options
    - ◊ For residents with reduced life expectancy, relatively low risk of cardiovascular events, or who are experiencing possible adverse effects, the decision to stop the statin should be considered. Stopping the statin may improve quality of life
    - ◊ In residents with a limited prognosis, statins should be stopped
    - ◊ Statins can usually be stopped without the need for tapering

! It is important to be aware of all drug interactions when discontinuing or decreasing the dose of a statin, as dose adjustments or increased monitoring of other medications may be required.

Figure 1. Benefits and harms of statins[24]

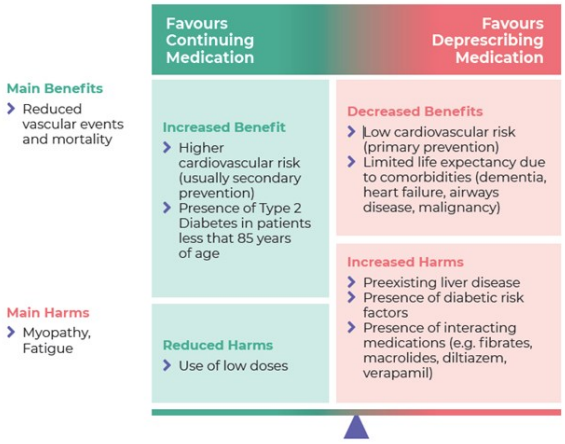

Table 2. Statin Intensity Dosage Options[13]

INTENSITY	STATIN OPTIONS
Low	Pravastatin 10-20 mg; lovastatin 10-20 mg; simvastatin 5-10 mg; atorvastatin 5 mg; rosuvastatin 2.5 mg
Moderate	Pravastatin 40-80 mg; lovastatin 40-80 mg; simvastatin 20-40 mg; atorvastatin 10-20 mg; rosuvastatin 5-10 mg
High	Atorvastatin 40-80 mg; rosuvastatin 20-40 mg

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References

1) Rabi, D. M., McBrien, K. A., Sapir-Pichhadze, R., Nakhla, M., Ahmed, S. B., Dumanski, S. M., Butalia, S., Leung, A. A., Harris, K. C., Cloutier, L., Zarnke, K. B., Ruzicka, M., Hiremath, S., Feldman, R. D., Tobe, S. W., Campbell, T. S., Bacon, S. L., Nerenberg, K. A., Dresser, G. K., Fournier, A., … Daskalopoulou, S. S. (2020). Hypertension Canada's 2020 Comprehensive Guidelines for the Prevention, Diagnosis, Risk Assessment, and Treatment of Hypertension in Adults and Children. *The Canadian journal of cardiology*, *36*(5), 596–624. https://doi.org/10.1016/j.cjca.2020.02.086
2) Wein, T., Lindsay, M. P., Gladstone, D. J., Poppe, A., Bell, A., Casaubon, L. K., Foley, N., Coutts, S. B., Cox, J., Douketis, J., Field, T., Gioia, L., Habert, J., Lang, E., Mehta, S. R., Papoushek, C., Semchuk, W., Sharma, M., Udell, J. A., Lawrence, S., … Heart and Stroke Foundation of Canada in collaboration with the Canadian Stroke Consortium (2020). Canadian Stroke Best Practice Recommendations, seventh edition: acetylsalicylic acid for prevention of vascular events. *CMAJ : Canadian Medical Association journal = journal de l'Association medicale canadienne*, *192*(12), E302–E311. https://doi.org/10.1503/cmaj.191599
3) By the 2019 American Geriatrics Society Beers Criteria® Update Expert Panel (2019). American Geriatrics Society 2019 Updated AGS Beers Criteria® for Potentially Inappropriate Medication Use in Older Adults. *Journal of the American Geriatrics Society*, *67*(4), 674–694. https://doi.org/10.1111/jgs.15767
4) Kosar, L., Jin, M. (2019). ASA for primary prevention of cardiovascular disease. *RxFiles.* https://www.rxfiles.ca/rxfiles/uploads/documents/ASA-Q%20and%20A-When%20to%20prescribe.pdf
5) McNeil, J. J., Wolfe, R., Woods, R. L., Tonkin, A. M., Donnan, G. A., Nelson, M. R., Reid, C. M., Lockery, J. E., Kirpach, B., Storey, E., Shah, R. C., Williamson, J. D., Margolis, K. L., Ernst, M. E., Abhayaratna, W. P., Stocks, N., Fitzgerald, S. M., Orchard, S. G., Trevaks, R. E., Beilin, L. J., … ASPREE Investigator Group (2018). Effect of Aspirin on Cardiovascular Events and Bleeding in the Healthy Elderly. *The New England journal of medicine*, *379*(16), 1509–1518. https://doi.org/10.1056/NEJMoa1805819
6) ASCEND Study Collaborative Group, Bowman, L., Mafham, M., Wallendszus, K., Stevens, W., Buck, G., Barton, J., Murphy, K., Aung, T., Haynes, R., Cox, J., Murawska, A., Young, A., Lay, M., Chen, F., Sammons, E., Waters, E., Adler, A., Bodansky, J., Farmer, A., … Armitage, J. (2018). Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. *The New England journal of medicine*, *379*(16), 1529–1539. https://doi.org/10.1056/NEJMoa1804988
7) Gaziano, J. M., Brotons, C., Coppolecchia, R., Cricelli, C., Darius, H., Gorelick, P. B., Howard, G., Pearson, T. A., Rothwell, P. M., Ruilope, L. M., Tendera, M., Tognoni, G., & ARRIVE Executive Committee (2018). Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. *Lancet (London, England)*, *392*(10152), 1036–1046. https://doi.org/10.1016/S0140-6736(18)31924-X
8) Mahmoud, A. N., Gad, M. M., Elgendy, A. Y., Elgendy, I. Y., & Bavry, A. A. (2019). Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. *European heart journal*, *40*(7), 607–617. https://doi.org/10.1093/eurheartj/ehy813
9) Zheng, S. L., & Roddick, A. J. (2019). Association of Aspirin Use for Primary Prevention With Cardiovascular Events and Bleeding Events: A Systematic Review and Meta-analysis. *JAMA*, *321*(3), 277–287. https://doi.org/10.1001/jama.2018.20578
10) Abdelaziz, H. K., Saad, M., Pothineni, N., Megaly, M., Potluri, R., Saleh, M., Kon, D., Roberts, D. H., Bhatt, D. L., Aronow, H. D., Abbott, J. D., & Mehta, J. L. (2019). Aspirin for Primary Prevention of Cardiovascular Events. *Journal of the American College of Cardiology*, *73*(23), 2915–2929. https://doi.org/10.1016/j.jacc.2019.03.501
11) Pearson, G. J., Thanassoulis, G., Anderson, T. J., Barry, A. R., Couture, P., Dayan, N., Francis, G. A., Genest, J., Grégoire, J., Grover, S. A., Gupta, M., Hegele, R. A., Lau, D., Leiter, L. A., Leung, A. A., Lonn, E., Mancini, G., Manjoo, P., McPherson, R., Ngui, D., … Wray, W. (2021). 2021 Canadian Cardiovascular Society Guidelines for the Management of Dyslipidemia for the Prevention of Cardiovascular Disease in Adults. *The Canadian journal of cardiology*, *37*(8), 1129–1150. https://doi.org/10.1016/j.cjca.2021.03.016
12) RxFiles Academic Detailing (2019). Dyslipidemia in Older Adults. *Geri-Rx Files: Assessing Medications in older adults* (3rd edition). Saskatoon: Saskatoon City Hospital; 2019.
13) Allan, G. M., Lindblad, A. J., Comeau, A., Coppola, J., Hudson, B., Mannarino, M., McMinis, C., Padwal, R., Schelstraete, C., Zarnke, K., Garrison, S., Cotton, C., Korownyk, C., McCormack, J., Nickel, S., & Kolber, M. R. (2015). Simplified lipid guidelines: Prevention and management of cardiovascular disease in primary care. *Canadian family physician Medecin de famille canadien*, *61* (10), 857–e450.
14) Han, B. H., Sutin, D., Williamson, J. D., Davis, B. R., Piller, L. B., Pervin, H., Pressel, S. L., Blaum, C. S., & ALLHAT Collaborative Research Group (2017). Effect of Statin Treatment vs Usual Care on Primary Cardiovascular Prevention Among Older Adults: The ALLHAT-LLT Randomized Clinical Trial. *JAMA internal medicine*, *177*(7), 955–965. https://doi.org/10.1001/jamainternmed.2017.1442
15) Gencer, B., Marston, N. A., Im, K., Cannon, C. P., Sever, P., Keech, A., Braunwald, E., Giugliano, R. P., & Sabatine, M. S. (2020). Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials. *Lancet (London, England)*, *396*(10263), 1637–1643. https://doi.org/10.1016/S0140-6736(20)32332-1
16) Grundy, S. M., Stone, N. J., Bailey, A. L., Beam, C., Birtcher, K. K., Blumenthal, R. S., Braun, L. T., de Ferranti, S., Faiella-Tommasino, J., Forman, D. E., Goldberg, R., Heidenreich, P. A., Hlatky, M. A., Jones, D. W., Lloyd-Jones, D., Lopez-Pajares, N., Ndumele, C. E., Orringer, C. E., Peralta, C. A., Saseen, J. J., … Yeboah, J. (2019). 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA Guideline on the Management of Blood Cholesterol: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Journal of the American College of Cardiology*, *73*(24), 3168–3209. https://doi.org/10.1016/j.jacc.2018.11.002
17) Ridker, P. M., Lonn, E., Paynter, N. P., Glynn, R., & Yusuf, S. (2017). Primary Prevention With Statin Therapy in the Elderly: New Meta-Analyses From the Contemporary JUPITER and HOPE-3 Randomized Trials. *Circulation*, *135*(20), 1979–1981. https://doi.org/10.1161/CIRCULATIONAHA.117.028271
18) Savarese, G., Gotto, A. M., Jr, Paolillo, S., D'Amore, C., Losco, T., Musella, F., Scala, O., Marciano, C., Ruggiero, D., Marsico, F., De Luca, G., Trimarco, B., & Perrone-Filardi, P. (2013). Benefits of statins in elderly subjects without established cardiovascular disease: a meta-analysis. *Journal of the American College of Cardiology*, *62*(22), 2090–2099. https://doi.org/10.1016/j.jacc.2013.07.069
19) Shepherd, J., Blauw, G. J., Murphy, M. B., Bollen, E. L., Buckley, B. M., Cobbe, S. M., Ford, I., Gaw, A., Hyland, M., Jukema, J. W., Kamper, A. M., Macfarlane, P. W., Meinders, A. E., Norrie, J., Packard, C. J., Perry, I. J., Stott, D. J., Sweeney, B. J., Twomey, C., Westendorp, R. G., … PROSPER study group. PROspective Study of Pravastatin in the Elderly at Risk (2002). Pravastatin in elderly individuals at risk of vascular disease (PROSPER): a randomised controlled trial. *Lancet (London, England)*, *360*(9346), 1623–1630. https://doi.org/10.1016/s0140-6736(02)11600-x
20) Ramos, R., Comas-Cufí, M., Martí-Lluch, R., Balló, E., Ponjoan, A., Alves-Cabratosa, L., Blanch, J., Marrugat, J., Elosua, R., Grau, M., Elosua-Bayes, M., García-Ortiz, L., & Garcia-Gil, M. (2018). Statins for primary prevention of cardiovascular events and mortality in old and very old adults with and without type 2 diabetes: retrospective cohort study. *BMJ (Clinical research ed.)*, *362*, k3359. https://doi.org/10.1136/bmj.k3359
21) Kutner, J. S., Blatchford, P. J., Taylor, D. H., Jr, Ritchie, C. S., Bull, J. H., Fairclough, D. L., Hanson, L. C., LeBlanc, T. W., Samsa, G. P., Wolf, S., Aziz, N. M., Currow, D. C., Ferrell, B., Wagner-Johnston, N., Zafar, S. Y., Cleary, J. F., Dev, S., Goode, P. S., Kamal, A. H., Kassner, C., … Abernethy, A. P. (2015). Safety and benefit of discontinuing statin therapy in the setting of advanced, life-limiting illness: a randomized clinical trial. *JAMA internal medicine*, *175*(5), 691–700. https://doi.org/10.1001/jamainternmed.2015.0289
22) Jensen, B., Regier, L. (2019). Lipid Lowering Therapy: Drug Comparison Chart. *RxFiles: Drug Comparison Charts* (13th Edition). Saskatoon: Saskatoon City Hospital.
23) Lexicomp (n.d.) Lexicomp: Interactions. *UpToDate.*
24) Tenni, P., Dunbabin, D., Deprescribing Reference Group. (2019). A guide to deprescribing statins. *Primary Health Tasmania*. https://www.primaryhealthtas.com.au/wp-content/uploads/2018/09/A-Guide-to-Deprescribing-Statins-2019.pdf
25) Rosenson, R. S. (2021). Statins: Actions, side effects, and administration. *UpToDate.* https://www.uptodate.com/contents/statins-actions-side-effects-and-administration
26) Adhikari, A., Tripathy, S., Chuzi, S., Peterson, J., & Stone, N. J. (2021). Association between statin use and cognitive function: A systematic review of randomized clinical trials and observational studies. *Journal of clinical lipidology*, *15*(1), 22–32.e12. https://doi.org/10.1016/j.jacl.2020.10.007
27) Diabetes Canada Clinical Practice Guidelines Expert Committee, Stone JA, Houlden RL, Lin P, Udell JA, Verma S. Cardiovascular Protection in People With Diabetes. Can J Diabetes. 2018 Apr;42 Suppl 1:S162-S169
28) Arnett DK, Blumenthal RS, Albert MA, Buroker AB, et al. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation. 2019
29) Campitelli M.A,, Maxwell, C.J, et al. One-year survival and admission to hospital for cardiovascular events among older residents of long-term care facilities who were prescribed intensive- and moderate-dose statins CMAJ Jan 2019, 191 (2) E32-E39; **DOI:** 10.1503/cmaj.18085