the PRUDENT prescriber

Phil Mohler, M.D.

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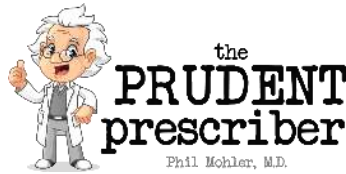**Statin Use for Primary Prevention Cardiovascular Disease Adults: A Guideline Run Amok?**

The USPSTF has recently updated their 2016 guidelines regarding use statin use as primary prevention for cardiovascular disease (CVD). Overall, the recommendations are largely unchanged. The United States Preventive Services Task Force (USPSTF) concluded with moderate certainty that statin use for the prevention of CVD events and all-cause mortality in adults aged 40 to 75 years with no history of CVD and who have one or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 10% or greater has at least a moderate net benefit.

In like manner the USPSTF concludes with moderate certainty that statin use for the prevention of CVD events and all-cause mortality in adults aged 40 to 75 years with no history of CVD and who have one or more CVD risk factors (dyslipidemia, and diabetes, hypertension, or smoking) and an estimated 10-year CVD event risk of 7.5% to less than 10% has at least a small net benefit. The decision to initiate therapy should depend on individual patient preference for a potential small benefit relative to the potential harms and inconvenience of taking a daily medication.

Finally, the USPSTF concludes that evidence is insufficient to determine the balance of benefits and harms of statin use for primary prevention of CVD events and mortality in adults 75 years or older with no history of CVD.

Population	USPSTF Recommendation	Grade
Adults ages 40 to 75 years who have one or more CV risk factors and an estimated 10-year cardiovascular disease risk of 10% or greater	Recommends that clinicians prescribe a statin for the primary prevention of CVD for adults ages 40 to 75 years with one or more CVD risk factors (dyslipidemia, diabetes, hypertension, or smoking) and estimated 10-year risk of a cardiovascular event of 10% or greater.	B
Adults ages 40 to 75 years who have one or more cardiovascular risk factors and an estimated 10-years CVD risk of 7.5% to less than 10%.	Recommends a clinician *selectively* offer a statin for the primary prevention of CVD for adults aged 40 to 75 years with one or more CVD risk factors and an estimated 10-yearto risk of a cardiovascular event of 7.5% to less than 10%. The likelihood of benefit is smaller in this group than in persons with a 10-year risk of 10% or greater.	C
Adults 76 years or older	The USPSTF concludes that the current evidence is insufficient to assess the balance of benefits and harms of initiating a statin for the primary prevention of CVD events and mortality and adult 76 years or older.	I

B=Offer or provide this service.
C=Offer or provide this service for selected patients depending on individual circumstances.
I=If the service is offered, patients should understand the uncertainly about the balance of benefits and harms.

Nuts and bolts of these recommendations:
- The USPSTF reviewed 22 trials reporting on the benefits of statin use for primary prevention. Mean duration of follow up was 3.3 years.
- There is limited evidence that suggests underprediction of the ACC/AHA risk estimator in disadvantaged communities. This might lead to underutilization of preventive therapies.
- As we have noted in previous editions, this risk estimator is imprecise and may lead to overestimation of risk in some populations.
- A majority of the trials reviewed by the USPSTF used fixed dose moderate–intensity statin therapy.
- There are no trials in this review to suggest that fixed dose statin or statin dosing to a certain LDL target is superior.
- Compared with the 2016 USPSTF review, the estimated benefit of statin therapy on mortality in this population was smaller.

Results of trials:
- Benefits of treatment

  - NNT to prevent one all cause death after 1-6 years (18 trials, n=85,186) = 286
  - NNT to prevent one fatal or non-fatal stroke after 1-6 years (15 trials, n=6,610) =256
  - NNT to prevent one fatal or non-fatal MI after 2-6 years (12 trials, n=75,401) =118
  - NNT to prevent one composite cardiovascular outcome after 1-6 years (15 trials, n=74,390) =78
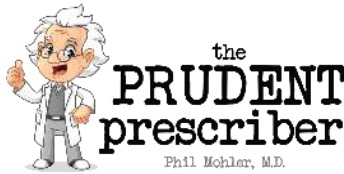
- Harms of treatment
  - Statin therapy vs placebo or no statin was not associated with increased risk of study withdrawal due to adverse events.
  - Statin therapy was not associated with increased risk of myopathy or rhabdomyolysis.
  - Statin therapy was not associated with any cancer or incident diabetes, but one study from the 2016 review showed that statin use was associated with an increased risk of cataract surgery (NNH= 143).

MY TAKE

- Reading this guideline fractured my long-standing belief that statins were associated with significant muscle side effects. These large randomized controlled studies suggest that once again we have been led astray by observational data.
- Although statins are safe and cheap, the NNTs are too high for my blood.
- I'm a little flummoxed by the lack of supporting data for using a fixed dose statin in most of these studies.
- I'm concerned that the ACC/AHA risk calculator overestimates risk in Caucasians and underestimates risk in people of color.
- There is also the paradoxical effect of not treating patients with high LDLs, but with less than > 10% or > 7.5% 10-year risk of a cardiovascular event. Conversely there is the inappropriate effect of treating someone with an elevated 10-year risk of an event, but with a low/normal LDL.
- I recall an era when there were incentives to apply the cardiovascular risk estimator to all patients. Is this algorithm worth the precious exam room time it takes to calculate the risk and then describe the intervention to the patient?
- This guideline simply does not feel "right" to me. I'm interested in your feedback. Is this a guideline that you have used, or would consider using in the future? What's wrong with my arguments against this intervention? Email me at pmohler69@gmail.com.

Medicare Drug Pricing: Breaking the Bonds of Avaricious Big Pharma

In August 2022, Congress enacted prescription drug pricing reforms as part of the Inflation Reduction Act (IRA). The law allows Medicare to directly negotiate prices for certain drugs, limit price increases and reduce out of pocket cost for part D beneficiaries. The IRA authorizes the Department of Health and Human Services to negotiate prices for a limited number of brand-name drugs with the greatest spending under part B and part D. The legislation limits the number of drugs that can be negotiated to 10 annually starting in 2026, increasing to 20 drugs annually by 2029. Secondly, a provision of the IRA will penalize manufactures that increase drug prices faster than inflation, starting in October 2022. Finally, the act includes some changes to improve medication affordability for Medicare part D beneficiaries. Starting in 2024, annual out-of-pocket costs will be capped, and more low-income Medicare beneficiaries will qualify for subsidized out-of-pocket costs.

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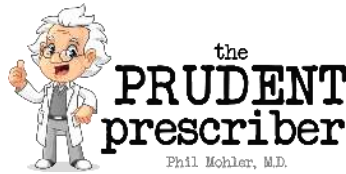
Which drugs will qualify in 2026? I read four different analyses of the drug selection and became progressively confused. It may take a Philadelphia lawyer to figure this out. PharmacyChecker.com, the internet-based resource for buying less costly Canadian and other country's drugs, has sorted through the legalese and predicts:

### Drugs Likely Eligible for Negotiated Medicare Pricing in 2026

Drug	Treatment	Total Medicare Spending in 2020
Eliquis (apixaban)	anticoagulant	$9,936,069,814
Januvia (sitagliptin phosphate)	diabetes	$3,86087,773
Imbruvia (ibrutinib)	leukemia	$2,962,909,304
Jardiance (empagliflozin)	diabetes	$2,376,166,292
Ibrance (Palbociclib)	breast cancer	$2,108,937,188
Xtandi (enzalutamide)	prostate cancer	$1,968567,948

 MY TAKE

- Yes, those are BILLION$ of dollar$!
- And yes, this is great news for patients although some of the rollout of this law is going to take a decade.
- With 61.6 million members, one would surmise that Medicare should have huge negotiating power. "We'll be paying Canadian prices (64% lower than average Medicare part D prices)."
- Unfortunately, that's probably not to be. Drug prices will be calculated on a "maximum fair price" depending on the time that has elapsed since FDA approval. It involves a calculation of a percentage of the drugs non-federal average manufacturing price for the first full year following its market entry along with a percentage increase in the consumer price index.

Short and Sweet

- **Acthar gel, the Pharmaceutical Outrage of the Month.** In June 2022, the folks at Goodrx explored (exposed) the 20 most expensive prescription drugs in the US. Coming in at *Number 11* was Acthar gel, manufactured by Mallinckrodt Pharmaceuticals. Acthar is used to treat lupus, rheumatoid arthritis, multiple sclerosis, infantile spasms, ophthalmic conditions and psoriatic arthritis. The real **OUTRAGE** is that in 2001 when the drug was still manufactured by Sanofi, the list price for one vial sold for about $40. Twenty-one years and a new manufacturer later, the list price for one vial (a typical one-month supply) of Acthar gel now runs **$41,459.**
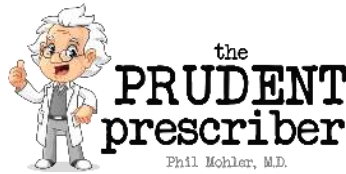
Update: on November 6, 2022, epocrates reports the price of one vial as $45,974.

- **Calf DVT-Surveillance or Anticoagulation?** A Mayo Clinic Proceedings (2021 May; 96;1184) real world study of 483 patients with ultrasound documented calf DVT suggests that propagation of the clot was less frequent in the vitamin K antagonist treated group (2.8%) vs (8.3%) in the surveillance group. NNT=18. There was no difference in the bleeding or mortality outcomes by management strategy. Net clinical benefit (the venous thromboembolism [VTE] recurrence plus major bleeding) favored anticoagulant therapy (9.8% versus 20 .2%) NNT=9.6. The results of the study corroborate a recent meta-analysis of randomized clinical trials (Cochrane Database Systemic Review 2020; 4:13422). The Cochrane study showed that treated patients had fewer VTEs (RR=0.34) and no difference in major bleeding episodes compared with the surveillance group. Anticoagulation with a vitamin K antagonist for three months or more compared with six weeks reduced the incidence of recurrent VTE from 13.9% to 5.8%.NNT=12.

- **Fluvoxamine for Covid-19** In the December 2021 Prudent Prescriber, I made a push for using the SSRI fluvoxamine off-label for mild- moderate Covid-19 based on a large Brazilian study. I was so convinced that of its efficacy that I solicited a prescription from my family doc for my own use. **I was wrong.** A subsequent analysis of that data (NEJM 2022 Aug18; 387:599) demonstrated the fallacies of the methods of that study. **Be Skeptical!**

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