

## Factsheet Statins

This factsheet can be used when considering the continuation or discontinuation of lipid-lowering agents (statins) in patients aged 70 years and older, in the context of cardiovascular risk, potential side effects, life expectancy, and frailty.

### Recommendations for reducing and stopping medication

#### Consider stopping statins in cases of:

- Limited estimated remaining life expectancy.
- Frail older adults:
  - With cardiovascular diseases if there is muscle pain.
  - Without cardiovascular diseases
- Older adults:
  - With cardiovascular diseases if there is muscle pain.
  - Without cardiovascular diseases if there is muscle pain. Without cardiovascular diseases concerning cardiovascular risk reduction.

#### Discontinuation strategy:

- A statin can be stopped abruptly.

#### Continue statins in

- Older adults with a very high risk of death from cardiovascular diseases, except in cases of limited estimated remaining life expectancy, frailty, or muscle pain.

## Recommendations for Reducing and Stopping Medication

### Consider stopping statins in cases of:

- **Limited estimated remaining life expectancy [Note 1]:**

The effect of stopping on cardiovascular risk in people with a limited estimated remaining life expectancy is minimal. Stopping statins in these people does not lead to extra cardiovascular events and mortality in the short term.

  - Stop statins.
- **Frail older adults:**
  - **With cardiovascular diseases if there is muscle pain [Note 3, 8]:**

Muscle pain-related complaints are a reason for 7-29% of statin users to stop.

    - Stop statins on a trial basis in case of muscle pain-related complaints.
    - Evaluate with the patient after 4 weeks if the complaints have disappeared.
    - If the complaints have disappeared after stopping, stop statins definitively.
    - If the complaints persist, consider restarting the same statin.
  - **Without cardiovascular diseases [Note 2]:**

In frail older adults without cardiovascular diseases, even in cases of severe dementia, it is unlikely that a statin still provides cardiovascular benefits.

    - Stop statins.
- **Older adults:**
  - **With cardiovascular diseases if there is muscle pain [Note 3, 8]:**

Muscle pain-related complaints are a reason for 7-29% of statin users to stop.

    - Stop statins on a trial basis in case of muscle pain-related complaints.
    - Evaluate with the patient after 4 weeks if the complaints have disappeared.
    - If the complaints have disappeared after stopping, stop statins definitively.
    - If the complaints persist, consider restarting the same statin.
    - If a second statin is not tolerated, dose a more potent statin every other day or multiple times a week.
    - If low dosing frequency is not tolerated, consider definitive discontinuation.
  - **Without cardiovascular diseases if there is muscle pain [Note 3, 8]:**

Muscle pain-related complaints are a reason for 7-29% of statin users to stop.

    - Stop statins on a trial basis in case of muscle pain-related complaints.
    - Evaluate with the patient after 4 weeks if the complaints have disappeared.
    - If the complaints have disappeared after stopping, consider stopping definitively.
    - If the complaints persist, consider restarting the same statin.
  - **Without cardiovascular diseases concerning cardiovascular risk reduction [Note 2, 4]:**

The effectiveness of statins is limited in older adults  $\geq 75$  years without cardiovascular diseases and in the absence of risk factors (diabetes, kidney damage).

    - Estimate the risk reduction by treatment with a statin by determining the cardiovascular risk with and without treatment goal.
    - Discuss the outcome with the patient and consider stopping or continuing in respect to the patient's wishes and avoiding polypharmacy.

### Method of tapering off:

- **A statin can be stopped abruptly [Note 7].**

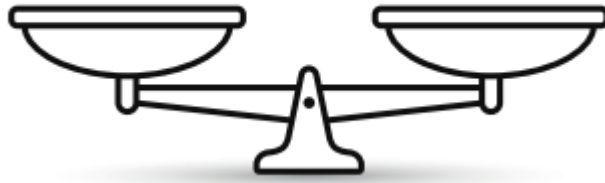
There is no tapering procedure required.

**Continue statins in the following cases:**

- **Older adults with a very high risk of death from cardiovascular diseases, except in cases of limited estimated remaining life expectancy, frailty, or side effects** [Note 4, 5].

Almost all older adults aged  $\geq 70$  years have a very high risk of death from cardiovascular diseases (10-year risk  $\geq 10\%$ ). Continue statins in patients with the following risk factors:

- Cardiovascular diseases; stopping a statin within 1 year after a myocardial infarction is associated with higher mortality.
- Diabetes mellitus with organ damage (e.g., diabetic retinopathy) or a significant risk factor (smoking, TC  $> 8$  mmol/l, blood pressure  $\geq 180$  mmHg). The risk of death from cardiovascular diseases is strongly increased. In diabetes without organ damage or risk factors, the risk is also increased, but less so [Note 4].
- Severe chronic kidney damage increases the risk of death from cardiovascular diseases in older adults, and moderate chronic kidney damage increases the risk to a lesser extent.
- Significantly elevated individual risk factors for death from cardiovascular diseases in older adults are smoking, TC  $> 8$  mmol/l, and blood pressure  $\geq 180$  mmHg.



### Considerations in favour of reducing and stopping

#### **Limited estimated remaining life expectancy:**

The effect of stopping on cardiovascular risk in people with a limited estimated remaining life expectancy is minimal. Stopping statins in these people does not lead to more cardiovascular events and mortality in the short term [Note 1].

#### **Frailty:**

In frail older adults without cardiovascular diseases, including patients with severe dementia, it is unlikely that a statin still provides cardiovascular benefits [Note 2].

#### **Muscle pain:**

In the presence of bothersome side effects such as muscle pain in the elderly, a trial stop of statins can be considered to determine causality [Note 3].

#### **Absence of cardiovascular diseases:**

The effectiveness of statins is limited in older adults  $\geq 75$  years without cardiovascular diseases and risk factors (diabetes, kidney damage) [Note 4].

#### **Patient's desire to stop:**

The desire to use fewer medications or to stop using statins.

### Considerations against reducing and stopping

#### **Independent daily functioning:**

Older adults who are independent in their daily functioning and do not have a limited estimated remaining life expectancy can continue using statins [Note 4, 5].

#### **Cardiovascular diseases:**

Stopping a statin within 1 year after a myocardial infarction is associated with higher mortality [Note 5].

#### **Diabetes mellitus:**

Diabetes mellitus with organ damage (diabetic retinopathy) or significant risk factors (smoking, TC  $> 8$  mmol/l, blood pressure  $\geq 180$  mmHg) increases the risk of death from cardiovascular diseases. Even in diabetes without organ damage or risk factors, the risk is increased, although less so [Note 4].

#### **Chronic kidney damage:**

Severe chronic kidney damage increases the risk of death from cardiovascular diseases in the elderly, and moderate chronic kidney damage increases the risk to a lesser extent.

#### **Significantly elevated risk factors:**

Certain risk factors (smoking, TC  $> 8$  mmol/l, blood pressure  $\geq 180$  mmHg) increase the risk of death from cardiovascular diseases.

#### **Long-term safety:**

Long-term studies have shown that statins are safe. If there are no or minimal side effects, there is no reason to stop [Note 6].

#### **Patient's desire to continue:**

The desire not to make changes to medication use.

## What is known about reducing and stopping statins in older adults?

### Limited estimated remaining life expectancy [Note 1]:

- Stopping statins in people with a limited estimated remaining life expectancy does not lead to more cardiovascular events and mortality in the short term.
- Statins are the most discontinued preventive medication in patients with a limited estimated remaining life expectancy.
- Despite this, over 30% of older adult cancer patients still use statins in the 30 days before death.

### Frail older adults [Note 2]:

- The proportion of older adults who stop using statins increases with age and frailty.
- The use of statins in older adults aged  $\geq 80$  years does not negatively affect the perceived health-related quality of life.

### Side effects [Note 3]:

- 7-29% of statin users discontinue treatment due to muscle-related side effects.

### Absence of cardiovascular diseases [Note 4]:

- Discontinuing statins in older adults without cardiovascular diseases is safe in the short term but does not improve quality of life or reduce healthcare costs.

## Notes

### Note [1]: Limited estimated remaining life expectancy

In a systematic review of studies on deprescribing cardiopreventive medication in patients with an estimated remaining life expectancy of 1-12 months, statins were the most discontinued type of medication, followed by aspirin and vitamin K antagonists. However, much preventive medication was continued until death [Narayan 2017]. An RCT showed that stopping statins does not lead to more mortality or cardiovascular events in the very short term (60 days) in people with limited life expectancy and may even improve quality of life [Kutner 2015]. In an observational study, over 30% of older adult cancer patients still used statins in the 30 days before death; for some of them, continuing statins unnecessarily contributed to the medication burden [Stavrou 2012].

### Note [2]: Frail older adults

The NHG Standard Cardiovascular Risk Management states: 'In people without known cardiovascular disease, the evidence that pharmacological prevention is effective becomes less convincing as people age. Especially for frail older adults, there is little evidence. This is particularly true for treatment with statins, where the beneficial effect in older adults over 75 years without cardiovascular disease must be considered uncertain' [CVRM 2017; Ramos 2018]. Consider less stringent target values for older or frail patients. Discontinuing preventive medication is indicated in case of side effects that are considered serious. In other cases, an individual assessment must be made for each patient, with avoiding polypharmacy and the patient's wishes as important considerations. Pharmacological prevention in older adults with known cardiovascular disease is supported by research and generally recommended unless frailty and side effects do not allow it or there is a limited expected life expectancy [Ramos 2018; Savarese 2013; Armitage 2019; Skolnik 2019]. Concerning life expectancy, the time to benefit should be considered. In the PROSPER study, a significant cardiovascular morbidity and mortality benefit was seen after an average of over 3 years of statin use (NNT 25). In several other studies with younger participants, a shorter time to benefit was found. In 2012, an 85-year-old man had an average remaining life expectancy of 5.6 years according to CBS. The life expectancy of an 85-year-old with cardiovascular disease for whom a statin is considered is likely lower and will mainly be determined by the severity of comorbidity and the current level of functioning [NHG 2019]. The same considerations apply to stopping a statin.

In a large database study in general practices in the United Kingdom, it was found that 5.6% of older adults aged  $\geq 80$  years stopped using statins, increasing to 17.8% at 100 years [Gulliford 2017]. The study also showed that the stopping rate in primary prevention (6.5%) was slightly higher than in secondary prevention (5.2%). The stopping rate also increased depending on the level of frailty, from 5.0% to 7.1% for the very frail.

Finnish research among statin users aged  $\geq 80$  years suggests that the use of statins does not negatively affect the perceived health-related quality of life compared to 80+ individuals who do not use statins [Strandberg 2018]. This refutes concerns about statin use in the oldest patients and indicates caution in reducing and stopping statins based solely on older age.

### Note [3]: Side effects

Safety data from clinical research show that statins are well tolerated, even by older patients [Baigent 2005; Gulliford 2017]. In practice, however, much higher percentages of patients report side effects of statins [Ramos 2018]. The most common side effect is muscle pain (myopathy).

*Myopathie/myalgia*

Myopathy, defined as a serum creatine kinase concentration  $> 10 \times$  the reference value, has been described as a side effect of statins in clinical trials and post-marketing reports in 0.1-0.5% of patients [NHG 2019]. The number of people who report muscle complaints (myalgia) in practice when using statins is 15-30%, and 7-29% of statin users stop statin treatment due to muscle-related side effects [Dalfsen 2017; Adel 2018]. In daily clinical practice, the risk of statin side effects in older adults, both with and without cardiovascular disease, is difficult to estimate. The absence of relevant myopathy in studies with statins cannot be extrapolated to daily practice: in these mostly pharmaceutical industry-sponsored studies, participants are often included who are more vital and have less comorbidity and co-medication than older adults who are now widely treated with statins. Post-marketing surveillance also does not provide a reliable indication of the incidence of myopathy, as it is often mild and partly affects older patients who already experience mobility disorders. However, mild myopathy can lead to a relevant reduction in mobility, which theoretically can even nullify the intended preventive effect [CVRM 2017]. Users of statins  $> 65$  years old do not have an increased risk of severe muscle-related side effects [Armitage 2019]. The most feared side effect, rhabdomyolysis (severe myopathy with muscle breakdown and myoglobinemia and myoglobinuria), is extremely rare: 0.44% per 100 patient-years [NHG 2019].

#### *Other side effects*

Mainly pravastatin and simvastatin have been associated in studies with the risk of fatigue and low energy levels, particularly in women [Golomb 2012]. Previous findings that lipid-lowering treatments may contribute to an increase in non-cardiovascular mortality (cancer, suicide, depression) or to mental disorders have not been confirmed in a large meta-analysis [NHG 2019; Emberson 2012].

#### **Note [4]: Absence of cardiovascular comorbidity**

For older adults aged 75-85 years without diabetes, statins have no effect on mortality and ischemic heart disease, and treatment does not seem meaningful [CVRM 2017; Ramos 2018; Savarese 2013; Armitage 2019; Skolnik 2019]. Recent French research suggests that stopping statins in older adults aged  $\geq 75$  years increases the risk of cardiovascular diseases by 33%, with the authors indicating that further research is desirable [Giral 2019].

For older adults aged 75-85 years with diabetes, it has been shown that treatment with statins reduces mortality and ischemic heart disease. In older adults aged  $> 85$  years, this effect seems to disappear, but the sample size was too small to establish this [Ramos 2018]. The Dutch ECSTATIC study ( $n = 1067$ , average age 55 years) showed that initially 65% of patients with a low cardiovascular risk ( $n = 492$ ) stopped preventive cardiovascular medication, and after 2 years, 27% were still stopped [Luymes 2018]. There was only a limited increase in systolic blood pressure (by 6 mmHg) and LDL cholesterol (by approximately 0.03 mmol/l). Annual monitoring of blood pressure and cholesterol makes stopping safe. A limitation of this study was the relatively young population with a very low 10-year risk of cardiovascular diseases.

#### **Note [5]: Cardiovascular diseases**

Statins have been proven effective in reducing mortality and cardiovascular events in people who already have cardiovascular disease, including older adults aged 65-75 years [Savarese 2013; Armitage 2019; Skolnik 2019]. There is limited evidence for the effectiveness of statins in older adults aged  $\geq 75$  years. See *Note 2*.

#### **Note [6]: Long-term safety**

Reduced cognition may be associated with statins, but a systematic review has not yet been able to demonstrate this association [Richardson 2013]. Further research is being conducted to determine

whether age directly influences the very small increase in diabetes among statin users and whether statins have an adverse effect on cognition [Armitage 2019].

**Note [7]: Stopping statins**

In Canada, it was found that stopping statins upon discharge from the hospital of admitted nursing home patients decreased from 26.4% in 2003-2004 to 10.6% in 2012 [Stall 2015]. In an Australian study, it was found that 95% of older hospital patients (average age 78 years) would be willing to stop their statin if their prescriber indicated that it was possible. The same percentage had concerns about possible side effects of statins [Qi 2015]. In American research, older adults (average age 72 years, n = 297) with limited life expectancy (1-12 months) mainly saw benefits in stopping statins, including lower costs (63%), the possibility of stopping other medications (34%), and improved quality of life (25%) [Tjia 2017].

**Note [8]: Trial stop of statins**

The Guideline on Hereditary Dyslipidemia in Secondary and Tertiary Care provides specific advice to assess troublesome side effects from statin use by alternating periods of 4 weeks with and without statin use. If myalgia recurs upon restarting, a more potent statin at a lower dose or lower frequency (e.g., every other day or even once a week) should be tried [NIV 2018]. The NHG Standard Cardiovascular Risk Management indicates that the management of a patient with myalgia but without a strong increase in creatine kinase in practice will be based on trial and error, where different statins are tried or a very low dose over several days per week, with a gradual increase in dosage [NHG 2019]. This advice has been followed in this knowledge document, where a different statin can also be tried upon reintroduction before a low dose of a more potent statin is tried. Depending on the situation (e.g., frail older adults), a direct decision can be made to stop statins after a trial stop.



## Literature

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**Authors and disclaimer**

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