Current status of treatments for cardiovascular aging: are statins a good option?

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Introduction

Cardiovascular (CV) **aging** involves all the changes that occur in the structure and functions of this system over the years resulting in well-defined phenotypic changes which render this system prone to disease.

The prevalence of age-related pathologies, such **as cardiovascular disease** (CVD), is increasing with the rising average age population constituting one of the fists causes of mortality. In consequence, better knowledge of the effect of aging on the CV system is needed for developing new and effective treatments in order to prevent or delay these alterations. Investigations targeting the arteries are bringing interesting results that may end in new treatments to prevent CV aging and, consequently, CVD.

Aims

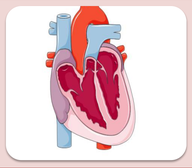
- To compile the current knowledge about the process of CV aging: changes that occur and the mechanisms involved.
- To analyse the scientific evidences of the use of statins for prevention of arterial aging.

Materials and Methods

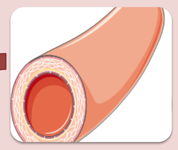
- **Search on PubMed database**: scientific literature including published reviews and papers.
- **Criteria of selection**: key words, quality and publication date.
- **Key words**: “cardiovascular”, “aging”, “senescence”, “arterial stiffness”, “pharmacological treatment”, “drugs” and “statins”.

Aging in the Cardiovascular System

Main Changes in the Cardiovascular System with Aging



- Loss of myocytes and hypertrophy of the remaining ones
- Reduction in the number of peacemaker cells
- Diastolic dysfunction
- ↓ maximal heart rate, maximal cardiac output and maximal VO_2



- Endothelial dysfunction
- Arteriosclerosis
- Arterial stiffness
- ↑ systolic arterial pressure

Figure 1. Images extracted from: [1].

Arterial Aging

- Changes in intimal and medial layers in large-sized and medium-sized arteries.
- 1st sign of CV system degeneration.
- **Arterial stiffness**:
  - Collagen deposition and elastin fragmentation in the subendothelial space due to repeated mechanical stress.
  - Measured with pulse wave velocity (PWV):

↑PWV ⇒ ↑ arterial stiffness ⇒ ↑ risk of CV events

Mechanisms Involved in Arterial Aging

Aging → Increased oxidants / Decreased antioxidant defense/ Angiotensin II/ Pro-inflammatory factors

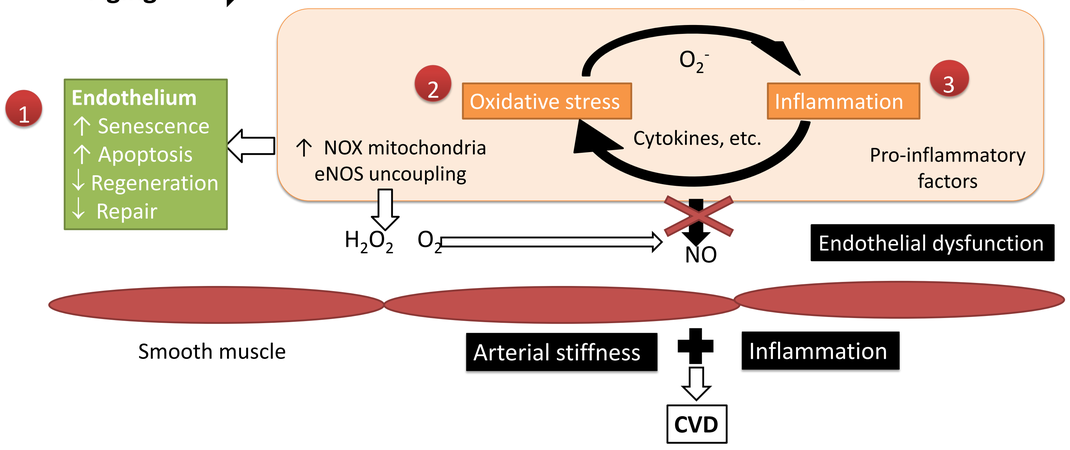


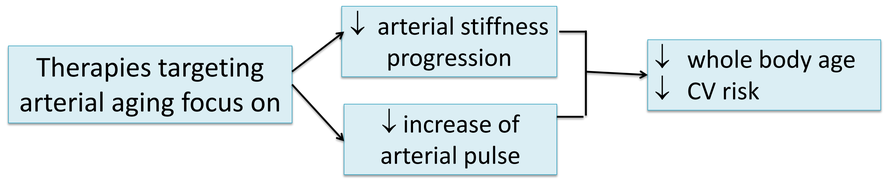
Figure 2. General perspective of the chain of events linking aging to CVD. Figure adapted from [2].

1. **Endothelium changes:** important role in arterial aging. Endothelial cell turnover and oxidative stress induce telomere shortening and, consequently, cell senescence.
2. **Oxidative stress:** the free radical theory of aging states that organisms age because of the production of intracellular reactive oxygen species (ROS) over time because there is an imbalance between the oxidative and anti-oxidative system. The two main causes of decreased expression of eNOS (endothelial nitric oxide synthase) are:
   - ↑ degradation of L-arginine, a major eNOS substrate, by arginase II.
   - ↑ degradation of tetrahydrobiopterin (BH_4), an important cofactor for eNOS activity, by oxidative stress.
3. "**Inflammaging**“: upregulation of the inflammatory response with progressing old age → vasculature is more susceptible to atherogenesis. It also stimulates the rupture of atherosclerotic plaques.

Therapeutic Strategies Targeting Arterial Aging

Strategies Targeting Arterial Aging

Arterial system is considered as a suitable target for anti-aging strategies because it connects all the organs in the body. Middle-aged individuals already present age-related reversible arterial wall changes that progress with aging, underlying the development of CVD.



Evidence of the Use Of Statins in Arterial Aging

Statins

- Main use: plasma cholesterol reduction → HMG CoA-reductase inhibitors
- Other beneficial pleiotropic effects

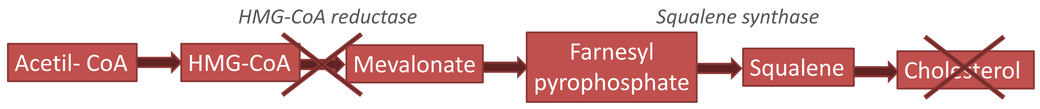


Fig. 3 Diagram representing the steps in cholesterol synthesis and the mechanisms of action of statins. Adapted from: [3].

- **Antioxidant properties**:
  - ↓ circulating LDL cholesterol and markers of oxidation
  - ↑ NO availability
- **↓ oxidative stress + inflammation** → destiffening properties
- **↑ circulating endothelial progenitors**
- **Stability of atherosclerotic plaques**:
  - ↓ accumulation of esterified cholesterol into macrophages
  - ↓ platelet clumping and aggregation

- **Benefits** for statin administration in reduction of arterial stiffness above CV risk reduction **have not been demonstrated**.
- **Treatment discontinuation** reduces the potential benefits and increases risk of adverse medication events.
- **Adverse reactions** in the muscular system, liver and kidneys. Different frequency of appearance, but often reported to be of low risk.
- **Lack of information about efficiency, safety and tolerability** when used for CV aging.

Conclusions

- Search of treatments targeting CV aging is of great importance for public health.
- Even though mechanisms of CV aging are almost fully understood, an even better understanding of the arterial aging process is needed.
- Reduction in arterial stiffness → decrease in arterial age → reduction in CV mortality and morbidity.
- There are still controversies about the use of statins or arterial aging and the mechanisms involved in their action.

Future Perspectives

Additional animal and human studies, especially long term prospective and larger studies, are required to confirm if statins administered preventively are able to:

- Reduce CV aging through improving arterial stiffness
- Reduce the incidence of CV events

References

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