Drugs that improve endothelial function.

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Endothelial dysfunction causes hypertension and vice-versa

Which one comes first?

Hypertension → Atherosclerosis

EC dysfunction → Arteriosclerosis

Atherosclerosis

Macrophage accumulation → Formation of necrotic core → Formation of fibrous cap

Arteriosclerosis

- Hardening of arteries
- Consequence of atherosclerosis + calcification
- Hypertension
- Endothelial dysfunction
- MI
- Aortic aneurysm
- Stroke

Endothelium

- Improve the bioavailability/release/mimic of endothelial mediators
- Decrease oxidative stress
- Increase/potentiate the downstream effect
Endothelial dysfunction causes hypertension and vice-versa

Which one comes first?

Hypertension

EC dysfunction

Atherosclerosis

Arteriosclerosis
Carvedilol

- First β-blocker to get FDA approval for heart failure
- Improves LV function, used in hypertension and heart failure
- Anti-oxidant activities: Long term months (no acute activities). Several metabolites of carvedilol (which have been found in human plasma) exhibit a much greater antioxidant activity than carvedilol itself (up to 50 times more activity)

Effects of Carvedilol Versus Metoprolol on Endothelial Function and Oxidative Stress in Patients With Type 2 Diabetes Mellitus. Am. Hypertension

Pharmacology of NO

What is the most profitable drug of all time?
Viagra

-Sildenafil (UK-92,480) was synthesized by Pfizer in England. It was initially studied for use in hypertension (high blood pressure) and angina pectoris (ischaemic cardiovascular disease).

Structure of Viagra

Viagra

cGMP
Mechanism of action

- Mechanism:
  1- parasympathetic nervous system causes NO release in the corpus cavernosum and leads to increased inflow of blood and erection.
  2- selective inhibitor of cGMP specific phosphodiesterase type 5 which is responsible for degradation of cGMP in the corpus cavernosum.

Revatio

Has anyone heard of Revatio?
Revatio

- Has anyone heard of Revatio?
- Used to treat pulmonary hypertension

Revatio

Mechanism of action?
Revatio and Viagra

Revatio

Viagra

Nitroglycerin
Nitroglycerin

Angina (mostly stable or unstable?)
Severe hypertension
Myocardial infarction

Do not use with viagra or revatio

Workers?

Murrell - 1879
He had unwittingly touched the moist cork stopper of a vial of nitroglycerin to his tongue while seeing outpatients. This caused a severe, pounding headache, tachycardia and a dramatic increase in the force of his heart beat.

Angiotensin II system
Angiotensin II

Angiotensin II has a direct negative effect on endothelial function:
- Decreases eNOS levels

Angiotensin II has an indirect negative effect on endothelial function:
- Oxidative stress

Angiotensin II has a direct effect on blood pressure:
- SMC Constriction

Angiotensin II has an indirect effect on blood pressure:
- Oxidative stress
Angiotensin II and Oxidative stress

Angiotensin II and Oxidative stress

Angiotensin II

HYPERTENSION

Intraluminal pressure

NADPH oxidase

AT1 vs AT2

NO synthase

Enzymatic uncoupling

Xanthine oxidase

Xanthine oxidase

LDL uptake

Endothelium

\[ \text{O}_2^- \rightarrow \text{H}_2\text{O}_2 \]

\[ \text{O}_2^- \rightarrow \text{ONOO}^- \]

\[ \text{O}_2^- \rightarrow \text{O}_2 \]

\[ \text{O}_2^- \rightarrow \text{H}_2\text{O}_2 \]

ANTIOXIDANT DEPLETION, LIPID PEROXIDATION, OXIDATIVE STRESS
Angiotensin II

Ang II inhibitors and direct effect on endothelial function

ACEi Increase NO function indirectly (less AngII oxidative stress) and directly (Bradykinin)
Angiotensin II

**Enzyme Inhibiting:**
- ACEI
  - Enhanced benefit from bradykinin accumulation (NO, vasodilatation)
  - Cannot inhibit non-ACE pathway (tissue chymase)
  - Cough (5%-40%)
  - Angioedema

**Receptor Blocking:**
- ARB
  - Selectively block AT₁ receptor
  - Completely block Ang II produced from all enzymatic pathways
  - Enhance AT₂ receptor stimulation (vasodilatation)
  - Angioedema

Angiotensin II and Oxidative stress

**AT₁**
- Blood pressure regulation
- Salt and water balance
- Sympathetic output
- Vascular and cardiac growth

**AT₂**
- Anti-AT₁
- Anti-proliferative/pro-apoptotic
- Tissue development and repair

**AT₃**
- Peptide degradation
- Anti-AT regulation of blood flow
- Net reabsorption
- Hypertrophy
- Memory and learning

Insulin oxytocin PKC-ε
Vascular Medicine

Rapid, Direct Effects of Statin Treatment on Arterial Redox State and Nitric Oxide Bioavailability in Human Atherosclerosis via Tetrahydrobiopterin-Mediated Endothelial Nitric Oxide Synthase Coupling

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Methods and Results—We first examined the association of statin treatment with vascular NO bioavailability and arterial superoxide (O₂⁻) in 492 patients undergoing coronary artery bypass graft surgery. Then, 42 statin-naïve patients undergoing elective coronary artery bypass graft surgery were randomised to atorvastatin 40 mg or placebo for 3 days before surgery to examine the impact of atorvastatin on endothelial function and O₂⁻ generation in internal mammary arteries. Finally, segments of internal mammary arteries from 20 patients were used in ex vivo experiments to evaluate the statin-dependent mechanisms regulating the vascular in situ state. Statin treatment was associated with improved vascular NO bioavailability and reduced O₂⁻ generation in internal mammary arteries. Oral atorvastatin increased vascular tetrahydrobiopterin bioavailability and reduced basal and fructose-1,6-diphosphate (FDP)-stimulated O₂⁻ in internal mammary arteries. In ex vivo experiments, atorvastatin rapidly improved vascular tetrahydrobiopterin bioavailability by upregulating GTP-cyclohydrolase I gene expression and activity, resulting in improved endothelial NO synthase coupling and reduced vascular O₂⁻. These effects were reversed by mevalonate, indicating a direct effect of vascular hydroxymethylglutaryl-coenzyme A reductase inhibition.

Conclusions—This study demonstrates for the first time in humans the direct effects of statin treatment on the vascular wall, supporting the notion that this effect is independent of low-density lipoprotein lowering. Atorvastatin directly improves vascular NO bioavailability and reduces vascular O₂⁻.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01013103.

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The online-only Data Supplement is available with this article at http://circ.ahajournals.org/cgi/content/full/CIRCULATIONAHA.110.985150/DC1.
Food supplement

-Vitamin C: Increase eNOS activity and decrease NADPH oxidase activity. Increases eNOS cofactor activity

-Vitamin E: Best anti-oxidant, but elusive activity

-All have been shown to reverse endothelial dysfunction in coronary of patients

-Poor clinical outcomes

-Polyphenols:
  -French paradox, Mediterranean diet 1992
  -50% lower CVD than North America
  -apples, blackberries, blueberries, cantaloupe, cherries, cranberries, grapes, pears, plums, raspberries, strawberries, vegetables, red wine, chocolate, green tea, olive oil
  -resveratrol

Polyphenols

-2 glasses a day (men)
-1 glass a day (women)
-Reduce oxidative stress
-Reduces LDL oxidation
-Increases HDL
-Resveratrol supplements
Flow-mediated dilatation (FMD) at baseline, 30, 60, and 120 min after the ingestion of the extract of red grapes or placebo. *P<0.001 versus baseline; **P<0.001 versus corresponding FMD at 60 min after the ingestion of the extract of red grapes.

Lekakis et al, Eur J Card Prev Rhabil