HMG-CoA Reductase Inhibitors

A Review of Pertinent Drug Information for SARS-CoV-2

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Data as of 05/01/2020

Objectives

- Briefly review the mechanism of action, safety issues and drug interactions of HMG-CoA reductase inhibitors (statins)
- Discuss the theoretical benefit of statin therapy in COVID-19
- Evaluate pertinent literature and future studies aimed at statin usage in COVID-19

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Explosion of Therapies

- **Antivirals**
  - Remdesivir*, Ribavirin*, Lopinavir/ritonavir*, Nitazoxanide, Oseltamivir, Baloxavir, Arbidol, Darunavir/cobicistat, Favipiravir, Nelfinavir, Sofosbuvir, Atazanavir
- **Antibiotics**
  - Doxycycline, Azithromycin
- **Immunotherapy**
  - Tocilizumab*, Anakinra*, Bevacizumab, Eculizumab, Sarilumab, TZLS-501 (anti-IL6R by Tiziana Life Sciences)
- **Cardiovascular/Anti-inflammatory**
  - ACEI/ARB*, Corticosteroids, NSAIDs*, HMG-CoA reductase inhibitors
- **Others**
  - Convalescent plasma*, Disulfiram, IVIG, Ivermectin, Ascorbic Acid, Zinc, Hydroxychloroquine*, Anti-coagulation

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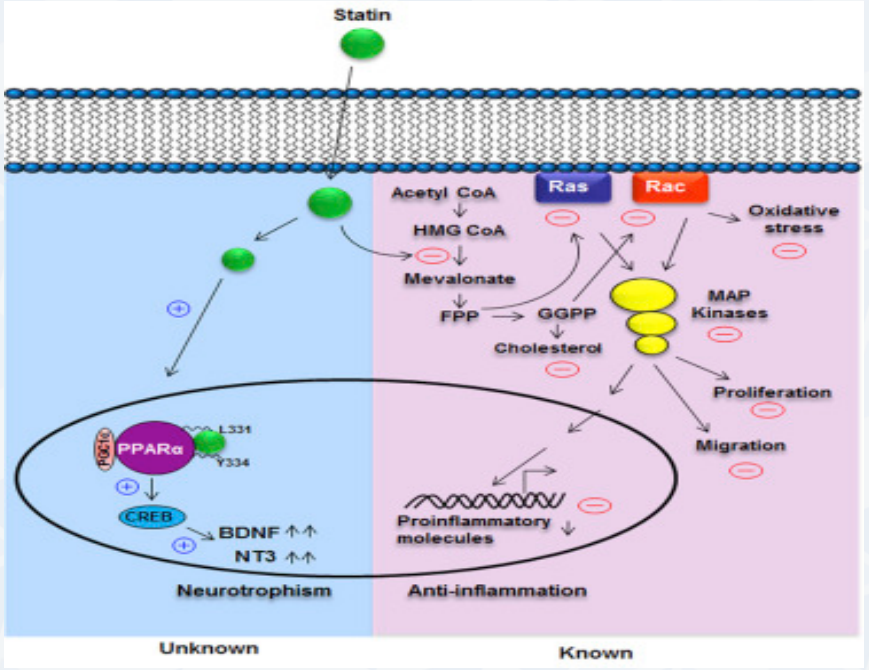
OFID 2020, ofaa105, doi/10.1093/ofid/ofaa105
COVID-19 Resources found at SIDP.org

Statin MOA

- Statins inhibit HMG-CoA reductase which is responsible for the conversion of HMG-CoA into Mevalonate
- Decrease in Mevalonate leads to decreased creation of cholesterol



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Goodman & Gilman's: The Pharmacological Basis of Therapeutics, 13th edition

Statin Adverse Effects

- Statin Associated Muscle Symptoms (SAMS)
  - Myalgia, myopathy
  - Myositis with elevated CK (creatinine kinase)
  - Rhabdomyolysis
- Hepatitis/Hepatic toxicity
- Renal toxicity
- Increased serum transaminases
- New onset DM Type 2

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Circulation Research. 2019;124(2): 328-350

Statin Drug Interactions

Statin	Metabolism	Drug Interactions
Atorvastatin	Substrate of CYP3A4 (major)	Lopinavir/ritonavir; Darunavir/cobicistat; Nelfinavir; Atazanavir; Tocilizumab; Sarilumab; Dabigatran; Warfarin; Azithromycin
Lovastatin	Substrate of CYP3A4 (major)	Lopinavir/ritonavir; Darunavir/cobicistat; Warfarin; Atazanavir; Tocilizumab; Sarilumab; Dabigatran; Azithromycin; Warfarin
Pravastatin	Substrate of CYP3A4 (minor)	Nelfinavir; Warfarin
Rosuvastatin	Substrate of CYP2C9 (minor)	Lopinavir/ritonavir; Darunavir/cobicistat; Nelfinavir; Atazanavir; Warfarin
Simvastatin	Substrate of CYP3A4 (major)	Lopinavir/ritonavir; Darunavir/cobicistat; Nelfinavir; Atazanavir; Azithromycin; Tocilizumab; Sarilumab; Dabigatran; Warfarin
Pitavastatin	Substrate of OATP1B1/SLCO1B1, UGT1A3, UGT2B7	Lopinavir/ritonavir; Darunavir/cobicistat; Atazanavir; Warfarin

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Drug Interactions. Lexicomp. Wolters Kluwer Health Inc. Riverwoods, Il. Available at: http://online.lexi.com. Accessed April 20, 2020.

Proposed Rationale for Statin Usage

- Cardiovascular element to COVID-19
- Statins and innate immunity
- Statins and viral pneumonia

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Cardiovascular Issues With COVID-19

Wang D[1]	N = 138 patients: CV disease found in 25% of patients in ICU vs. 10.8% non-ICU (p = 0.04) DM found in 22.2% in ICU vs. 5.9% non-ICU (p = 0.009)
Zhou F[2]	N = 191 patients: 31% of non-survivors had DM vs. 14% of survivors (p = 0.0051) 24% of non-survivors had CHD vs. 1% of survivors (p = <0.0001)
Guan W[3]	N = 1,099 patients: 16.2% of severe COVID had DM vs. 5.7% of non-severe 5.8% of severe had CAD vs. 1.8% of non-severe
Wu Z[4]	N = 72,314 patients: Overall Case Fatality Rate (CFR) was 2.3% CFR was 10-15% with CAD and 7.3% with DM
Italian NIH	N = 355 deaths: most common co-morbidity was 76% HTN, 36% DM and 33% CHD

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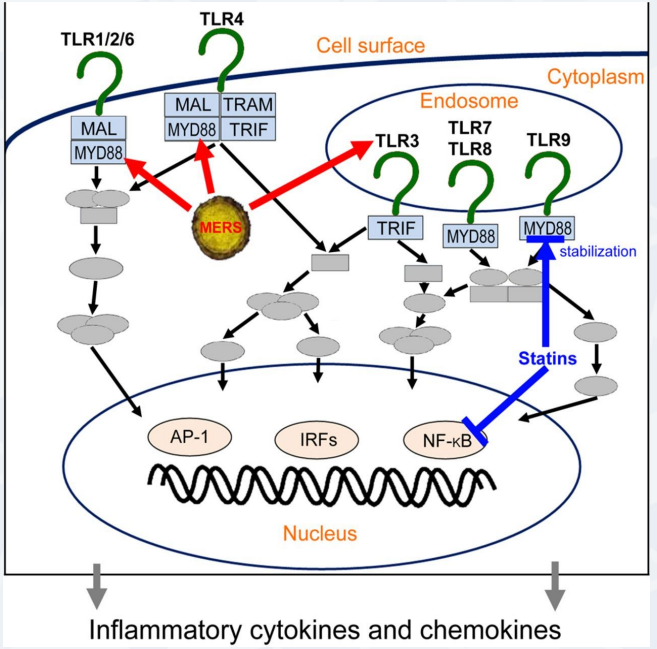
1. JAMA 2020;323(11):1061-69 2. Lancet 2020;395(10229):1054-62 3. NEJM 2020 doi:10.1056/NEJMoa2002032 4. JAMA 2020 doi: 10.1001/jama.2020.2648 5. Italian NIH

Innate Immunity

- Myeloid differentiation primary response 88 (MyD88)
  - Over-expression and under-expression were related to increased mortality after MERS-CoV infection[1]
- NF-kB
  - Activation can lead to increased inflammation via cytokines and chemokines[1]



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1. doi:10.1002/PHAR.2397 2. doi:10.1128/mBio.01120-15

Statins and Influenza

Trial	Trial Design	N	Statin Utilized	Outcomes
Frost, et al[1]	Matched cohort study and 2 case-control studies	N = 76,232 Case Control Studies N = 397 Influenza deaths N = 207 COPD deaths	No specific data Average daily dose was 10 mg/d Low daily dose < 4 mg/d Moderate daily dose ≥ 4 mg/d	For moderate dose statin usage, found significant reduced odds ratios of influenza/pneumonia death (OR, 0.60; 95% CI, 0.44-0.81) and COPD death (OR, 0.17; 95% CI, 0.07-0.42)
Vandermeer, et al[2]	Analysis of active surveillance	N = 3043 patients with laboratory confirmed influenza 1013 received statins 151 Died	No specific data	Administration of statins prior to or during hospitalization were associated with a protective odds of death (AOR, 0.59; 95% CI, 0.38-0.92)

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1. Chest 2007, 131(4):1006-12.
2. J Infect Dis, 2012, 205(1)13-9.

Statins and Influenza

Trial	Trial Design	N	Statin Utilized	Outcomes
Brett, et al[3]	Retrospective case-control study	N = 1520 with confirmed H1N1	No specific data	No significant association between pre-admission statin use and severity of outcome, (AOR, 0.81; 95% CI, 0.46-1.38)
Kwong, et al[4]	Population-based cohort study	N = 2,240,638 1,120,319 – statin group 1,120,319 – control group	- Atorvastatin - Simvastatin - Pravastatin - Other statins	Associated with a small protective effect for hospitalization (OR, 0.92; 95% CI, 0.89-0.95), 30-day pneumonia mortality (OR, 0.84; 95% CI, 0.77-0.91) and all-cause mortality (OR, 0.87; 95% CI, 0.84-0.89)

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3. PLoS One 2011. 25;6(4):e18120.
4. PLoS One 2009, 30;4(11):e8087

Statins and Sepsis/ARDS

Trial	Trial Design	Outcomes
Simvastatin in the Acute Respiratory Distress Syndrome[1]	Multicenter, double-blind clinical trial Simvastatin 80 mg daily or placebo for a maximum of 28 days	Although safe and associated with minimal adverse effects, no significant difference was found in ventilator free days (12.6 +/- 9.9 statin vs. 11.5 +/- 10.4 placebo, p = 0.21), days free of nonpulmonary organ failure (19.4 +/- 11.1 statin vs. 17.8 +/- 11.7, p = 0.11) or mortality at 28 days (22.0% statin vs. 26.8% placebo, p = 0.23)
Rosuvastatin for Sepsis-Associated Acute Respiratory Distress Syndrome[2]	Multicenter, double-blind randomized trial Rosuvastatin 40 mg loading dose then 20 mg daily versus placebo for a maximum of 28 days	Study was stopped early, no significant difference in 60 day in hospital mortality (28.5% rosuvastatin vs. 24.9% placebo, p 0.21) or ventilator free days (15 days rosuvastatin vs. 15 days placebo, p 0.96)

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1. NEJM 2014, 371:1695-1703.
2. NEJM 2014, 370:2191-2200

Clinical Trials

Study Name	Study Interventions	Study Enrollment and Outcomes
Preventing Cardiac Complication of COVID-19 Disease with Early Acute Coronary Syndrome Therapy: A Randomized Controlled Trial (C-19-ACS) **London** (NCT04333407)	Randomized, Parallel Assignment, Prospective Multicenter Randomized Controlled Trial **Intervention:** - Aspirin 75 mg daily - Clopidogrel 75 mg daily - Rivaroxaban 2.5 mg twice daily - ***Atorvastatin 40 mg daily*** **Control Arm:** No intervention	Target Enrollment: 3,170 participants (currently recruiting) Outcomes: ***Primary:*** - All-cause mortality at 30 days after admission ***Secondary:*** - Absolute change in serum troponin from admission to peak value - Discharge rate (at 7 and 30 days) - Intubation rate (at 7 and 30 days)

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https://clinicaltrials.gov/ct2/show/NCT04333407?term=statins&cond=covid+19&draw=2&rank=2

Clinical Trials

Study Name	Study Interventions	Study Enrollment and Outcomes
Study of Ruxolitinib Plus Simvastatin in the Prevention and Treatment of Respiratory Failure of COVID-19 **Spain** (NCT04348695)	Randomized, Parallel Assignment, Phase II Clinical Trial **Intervention:** - Ruxolitinib 5 mg orally q12h for 7 days, which will be increased to 10 mg q12h for a total of 14 days - ***Simvastatin 40 mg daily for 14 days*** **Control Arm:** No intervention	Target Enrollment: 94 participants (currently recruiting) Outcomes: ***Primary:*** - Percentage of patients who develop severe respiratory failure (7 days) ***Secondary:*** - Percentage of patients who develop severe respiratory failure (14 days); Length of ICU stay; Length of hospital stay; Survival rate at 28 days, 6 and 12 months and AE rates

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https://clinicaltrials.gov/ct2/show/NCT04348695?term=statins&cond=covid+19&draw=2&rank=1

Clinical Trials

Study Name	Study Interventions	Study Enrollment and Outcomes
Coronavirus Response – Active Support for Hospitalized COVID-19 Patients (CRASH-19) **London** (NCT04343001)	Randomized, Factorial Assignment, Multinational **Intervention:** **8 arms (7 active, 1 control)** - ASA monotherapy - Losartan monotherapy - ***Simvastatin monotherapy*** - ASA + Losartan - ***ASA + simvastatin*** - ***Losartan + Simvastatin*** - ***ASA + Losartan + Simvastatin*** **Control Arm:** No intervention	Target Enrollment: 10,000 participants (currently not recruiting) Outcomes: ***Primary:*** - Death (up to 28 days) ***Secondary:*** MI; Myocarditis; Resp. failure; viral pneumonitis; ARF; sepsis; stroke; GI bleed; Non invasive or invasive MV; ability to self care at discharge; arrhythmia; congestive cardiac failure (up to 28 days)

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https://clinicaltrials.gov/ct2/show/NCT04343001?term=statins&cond=covid+19&draw=2&rank=3

Summary

- Patients who are on statins should remain on their home regimen unless contraindicated
- Drug interactions can occur with a few of the proposed treatments for COVID-19
- Use caution in patients with sepsis induced hepatic injury
- There is no evidence or literature support for the addition of a statin specifically for COVID-19 therapy
- Currently there are 3 ongoing RCT's evaluating usage of statins in COVID-19, await results and evaluation prior to recommending statin therapy

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Data as of 4/30/2020