Do Statins Matter in the Treatment of Patients With P.E.?

Anthony J. Comerota, MD, FACS, FACC

Should all patients with VTE be treated with a statin

- Disclosures -

None

Pleiotrophic effects of statins: Inflammation

Statins Effect on Inflammation

- *Reduction: Neutrophil Extracellular Traps (NETs)*
- *Reduction thrombus MAC-3 levels*
- *Reduction Myeloperoxidase markers*
- *Reduced macrophage content*
- *Reduced MMP activity*
- *48 % reduction in vein wall scarring…..*
  …..Long-term implications

Kessinger CW et al.
PLOS ONE 2015;10(2):e0116621

Pleiotrophic effects of statins: Coagulation

Statin's Effect on Coagulation

- *Reduce clotting factors*
- *Increase endogenous fibrinolysis*
- *Reduce Tissue Factor*
- *Decrease platelet activation/aggregation*
- *Decrease endothelial cell adhesion molecules*

Semin Thromb Hemost 2019;45:825

Statins for the Management of VTE

We'll Examine

- Basic Science Studies
- Biomarker studies of coagulation / inflammation
- Large observational studies
- Meta-analyses / Systematic Reviews
- Randomized Trials: *Primary Prevention*
  Secondary Prevention
  Post-Thrombotic Syndrome

RESEARCH ARTICLE

Statins Improve the Resolution of Established Murine Venous Thrombosis: Reductions in Thrombus Burden and Vein Wall Scarring

Chase W. Kessinger[1‡], Jin Won Kim[1,2‡], Peter K. Henke[3], Brian Thompson[4], Jason R. McCarthy[5,6], Tetsuya Hara[1], Martin Sillesen[7], Ronan J. P. Margey[1], Peter Libby[8], Ralph Weissleder[5,6], Charles P. Lin[4,6], Farouc A. Jaffer[1,4,5]*

PLOS ONE 2015;10(2):e0116621

Statins Improve the Resolution of Established Murine Venous Thrombosis

Methods

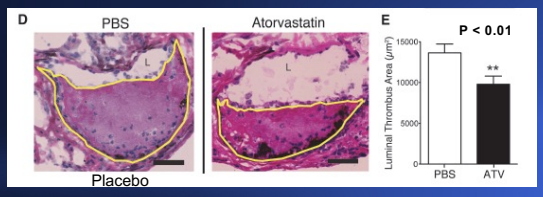
- Ferric Chloride model of murine femoral/saphenous venous thrombosis
- Stasis model of murine IVC thrombosis
- 24 hrs. after thrombosis, treatment randomized to statin vs. PBS (placebo)
- Intravital molecular-structural microscopy for changes in thrombus burden and inflammation

Kessinger CW et al.
PLOS ONE 2015;10(2):e0116621

Statins Improve the Resolution of Established Murine Venous Thrombosis

- Results @ Day 4 -

Treatment started 24 hrs. after thrombosis

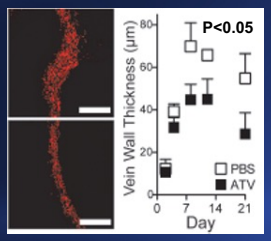


- Pro-Fibrinolytic Activity -

Kessinger CW et al.
PLOS ONE 2015;10(2):e0116621

Statins Improve the Resolution of Established Murine Venous Thrombosis

- Results @ Day 21 -



Reduction in thrombus burden and vein wall thickness suggest mechanisms for reduction in PTS.

Kessinger CW et al.
PLOS ONE 2015;10(2):e0116621

JUPITER Trial

The NEW ENGLAND JOURNAL of MEDICINE

- Primary Prevention -

ORIGINAL ARTICLE

A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

Robert J. Glynn, Sc.D., Eleanor Danielson, M.I.A., Francisco A.H. Fonseca, M.D., Jacques Genest, M.D., Antonio M. Gotto, Jr., M.D., John J.P. Kastelein, M.D., Wolfgang Koenig, M.D., Peter Libby, M.D., Alberto J. Lorenzatti, M.D., Jean G. MacFadyen, B.A., Børge G. Nordestgaard, M.D., James Shepherd, M.D., James T. Willerson, M.D., and Paul M Ridker, M.D.

NEJM 2009; 360:1851-61

A Randomized Trial of Rosuvastatin in the Prevention of Venous Thromboembolism

Glynn R J et al NEJM 2009; 360:1851-61

Results

– Blinded Results to Close-Out Visit –
(N=17,802)

	Events Per 100 Persons-Years			
	Rosuvas. (N=8901)	Placebo (N=8901)	HR	p-value
Venous Thromboembolism				
Total	*0.18*	*0.33*	*0.55*	*0.003*
Unprovoked	*0.10*	*0.18*	*0.59*	*0.06*
Provoked	*0.08*	*0.16*	*0.50*	*0.02*
Pulmonary Embolism	0.09	0.12	0.71	*0.27*
Deep-Vein Thrombosis	0.09	0.21	0.45	*0.003*

No association of VTE with lipid levels

Statins and primary prevention of venous thromboembolism: a systematic review and meta-analysis

Setor K Kunutsor, Samuel Seidu, Kamlesh Khunti

Lancet Haematol 2017;4:e83-93

- *36 eligible studies; 3,148,259 subjects*
- *23 RCTs, statins vs. placebo; 118,464 subjects*

- Results -

- Observation Studies - *RR for VTE: 0.75 p<0.0001*
- RCTs – *RR for VTE: 0.85 p=0.038*
- Rosuvastatin has lowest risk of VTE vs. other statins: *RR for VTE: 0.57 p=0.015*

Statin Treatment and the Risk of Recurrent Pulmonary Embolism

- Secondary Prevention -

S. Biere-Rafi, et al., Eur. Heart J 2013;34:1800

Methods

- Data: PHARMO Record Linkage System
  Utrecht, Netherlands. Links Hospital & Pharmacy records.
- ***All patients in Netherlands are included in system.***
- Patients: *1st Hosp. for P.E.; 1998 – 2008*
  (In Netherlands, all PE Rx'ed as inpatient)
- Statins and Chol. level recorded

Data analyzed according to Statin Treatment, dose and duration.

- Outcomes -

Primary: ***Symptomatic Recurrent P.E.***

Secondary: CV Events; All-cause mortality

Statin Treatment and the Risk of Recurrent Pulmonary Embolism

S. Biere-Rafi, et al., Eur. Heart J 2013;34:1800

Results: *Protective Effect of Statins*

	Recurrence	
Group	*No Statins*	*Statins*
During VKA	*2.18%*	*0.62%* *H.R. = 0.22*
After VKA	*8.38%*	*4.42%* *H.R. = 0.53*
Overall	*10.56%*	*5.04%* *H.R. = 0.48*

<0.01>p<0.001

Statin Treatment and the Risk of Recurrent Pulmonary Embolism

S. Biere-Rafi, et al., Eur. Heart J 2013;34:1800

Outcome vs. Intensity of Statin Rx.

–Expressed by LDL-C Reduction–

Reduction of LDL-C *(Potency of Statin)*	***Endpoint (H.R.) Recurrence***
<20%	0.88
20 – 40%	0.44
>40%	0.29* *p<0.001*

****71% reduction in recurrent PE – "Dose Response"***

Effects of Rosuvastatin as an adjuvant treatment for deep vein thrombosis

San Norebeto EM, Gastambide MV, Taylor JH, Garcia-Saiz I, Vaquero C.

Vasa 2016;45(2):133-40

Hypothesis

The addition of rosuvastatin to LMWH Rx of acute DVT reduces inflammation and risk of PTS.

Design - RCT

- ***230 subjects with acute DVT, randomized to: LMWH vs. LMWH+statin***
- ***Endpoints: Inflammation (CRP levels) Villalta Score/Post-thrombotic Syn.***

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Effects of Rosuvastatin as an adjuvant treatment for deep vein thrombosis

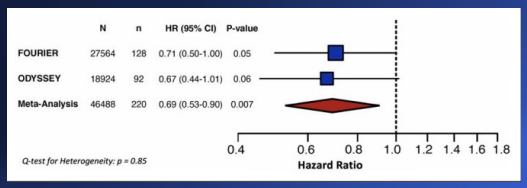
Results

Endpoints	LMWH (N=116)	LMWH+Statin (N=118)	p-value
CRP (mg/dL)	22.4	4.17	0.018
Villalta Score	5.58	3.45	0.035
PTS	48.5	38.3	0.019

Vasa 2016;45(2):133-40

The Effect of PCSK9 (Proprotein Convertase Subtilisin/Kexin Type 9) Inhibition on the Risk of Venous Thromboembolism

Effect of PCSK9 Inhibitors on VTE



HR – 0.69
P = 0.007

Marston NA et al
Circulation 2020;141:1600

Should All Patients With Acute Venous Thromboembolism Be Treated With A Statin?

Conclusions

- Basic Science Studies
- Biomarker studies of coagulation / inflammation
- Large observational studies
- Meta-analyses / Systematic Reviews
- Randomized Trials…….

……Unequivocally support the use of statins in all patients with acute VTE!

Should All Patients With Acute Venous Thromboembolism Be Treated With A Statin?

Yes!

Inova Heart and Vascular Institute

Thank you !