Does the morbidity and pathology of adverse events with atherosclerosis depend on Thrombosis? If so, does it explain the benefits of Rivaroxiban and ASA seen in the COMPASS and VOYAGER Trials.

Anthony J. Comerota, MD, FACS, FACC

The pathology of adverse events of atherosclerosis depends on thrombosis. Explaining results of Compass and Voyager Trials.

Disclosures

None

What is the pathology of PAD?

Atherosclerosis…..

…..causing luminal obstruction

Why do some patients develop Critical Limb Ischemia?

Traditional teaching: Ischemia is the consequence of progressive atherosclerotic disease causing arterial luminal obstruction.

There is more to the pathophysiology of atherosclerotic arterial luminal obstruction. Atherosclerosis….

….causes Endothelial Cell Dysfunction

….Endothelial Cell Dysfunction is associated with a significant Prothrombotic State

Prothrombotic State of Atherosclerosis

Intravascular Coagulation: Blinded Analysis

PAD Patients at Increased Risk

Assay	Controls *(N=41)*	PAD *(N=26)*	*P*-value
TF-PCA (U/ml)	22	127	<.0001
FVIIa (mU/ml)	58	100	<.0001
TAT (µg/L)	1.5	3.3	<.0001
F1.2 (nM)	1.3	1.55	<.0001

Rao AK, Comerota AJ, et al Thromb Haemost 2006;96:738

Can this prothrombotic state of atherosclerosis cause thrombosis of non-stenotic arteries?

YES!

Narula et al performed a study to investigate the etiology of arterial occlusion in patients with CLI requiring major limb amputation

Pathology of Peripheral Artery Disease in Critical Limb Ischemia

N Narula, AJ Dannenberg, JW Olin, DL Bhatt, KW Johnson, G Nadkarni, J Min, S Torii, P Poojary, SS Anand, JJ Bax, S Yusuff, R Vermani, J Narula

JACC 2018;72:2152-63

Purpose

- To describe the pathology of lower-extremity arteries in patients with major amputation from CLI
- To better understand the mechanisms leading to amputation in patients with CLI

Atherosclerosis vs. Thrombosis

Pathology of Peripheral Artery Disease in Critical Limb Ischemia

Methods

- **121 major limb amputations for CLI**
- **239 arteries; sectioned @ site of max. stenosis**
- **The contribution to stenosis quantified by both atherosclerotic plaque and thrombus**
- **Plaque classified by AHA classification**
  - ***Adaptive intimal thickening***
  - ***Pathologic intimal thickening***
  - ***Fibroatheroma***
  - ***Fibrocalcific plaque***

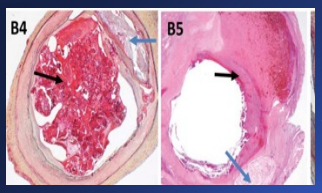
Navneet Narula et al. JACC 2018;72:2152-2163

Pathology of Peripheral Artery Disease in Critical Limb Ischemia

- Findings -

FC plaque 30% stenosis

Acute Occlusive Thrombus



Ulcerated/disrupted FC with necrotic core and luminal thrombus

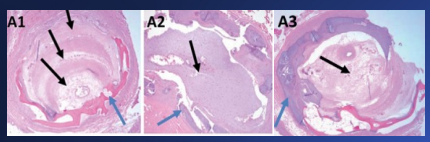
Thrombi in popliteal arteries
Plaque causes no significant stenosis

Navneet Narula et al. JACC 2018;72:2152-2163

Black arrows: Thrombus
Blue arrows: Fibrocalcific Plaque

Pathology of Peripheral Artery Disease in Critical Limb Ischemia

73 y.o. woman, BKA for CLI with gangrene, unreconstructable infrapop. occlusive disease



Post. Tibial *Ant. Tibial* *Peroneal*

Thrombi occludes each tibial artery ....
Plaque causes no significant stenosis

Navneet Narula et al. JACC 2018;72:2152-2163

Black arrows: Thrombus
Blue arrows: Ca++

Pathology of Peripheral Artery Disease in Critical Limb Ischemia

Results

Vessel Wall Pathology: CLI with >70% Stenosis

	Fem-Pop	Infra-Pop	OR	P Value
n	31	134		
Chronic Thrombi- insig.ASO	42%	81%	16.71	< 0.0001
Chronic Thrombi- sig. ASO	58%	19%		
Acute Thrombi- insig. ASO	33%	53%	0.71	0.41
Acute Thrombi- sig. ASO	67%	47%		

Navneet Narula et al. JACC 2018;72:2152-2163

Pathology of Peripheral Artery Disease in Critical Limb Ischemia

Thrombosis (acute and chronic) is an important part of the pathophysiology of critical limb ischemia….which raises the question….

Can *antithrombotic Rx reduce* ischemic events?

Navneet Narula et al.
JACC 2018;72:2152-2163

Pathology of Peripheral Artery Disease in Critical Limb Ischemia

The COMPASS and VOYAGER Trials were designed to answer that question!

Navneet Narula et al.
JACC 2018;72:2152-2163

COMPASS Trial

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

J.W. Eikelboom, S.J. Connolly, J. Bosch, G.R. Dagenais, R.G. Hart, O. Shestakovska, R. Diaz, M. Alings, E.M. Lonn, S.S. Anand, P. Widimsky, M. Hori, A. Avezum, L.S. Piegas, K.R.H. Branch, J. Probstfield, D.L. Bhatt, J. Zhu, Y. Liang, A.P. Maggioni, P. Lopez-Jaramillo, M. O'Donnell, A.K. Kakkar, K.A.A. Fox, A.N. Parkhomenko, G. Ertl, S. Störk, M. Keltai, L. Ryden, N. Pogosova, A.L. Dans, F. Lanas, P.J. Commerford, C. Torp-Pedersen, T.J. Guzik, P.B. Verhamme, D. Vinereanu, J.-H. Kim, A.M. Tonkin, B.S. Lewis, C. Felix, K. Yusoff, P.G. Steg, K.P. Metsarinne, N. Cook Bruns, F. Misselwitz, E. Chen, D. Leong, and S. Yusuf, for the COMPASS Investigators*

NEJM 2017;377:1319-30

Dual Pathway Inhibition vs. Monotherapy with a thrombin inhibitor or platelet inhibitor for reduction of ischemic events in patients with ***stable*** cardiovascular disease

COMPASS Trial

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

- Study -

- **27,395 patients with stable coronary, carotid or peripheral vascular disease**
- **Randomized: ASA 100 mg/da**
  Rivaroxaban 5.0 mg bid
  Rivaroxaban 2.5 mg bid + ASA 100 mg/da

Eikleboom JW., et al
NEJM 2017;377:1319

COMPASS Trial

- Primary Efficacy Outcome -

CV Death
Stroke
Myocardial Infarction

Eikleboom JW., et al
NEJM 2017;377:1319

COMPASS Trial

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

- Results -

Primary Composite Outcomes

- **24% reduction: Stroke, MI, CV death ($p < .001$)**
- **18% reduction in all-cause mortality**
- **No benefit from Rivaroxaban 5.0 mg bid**

Eikleboom JW., et al
NEJM 2017;377:1319

COMPASS Trial

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

*Sonia S Anand, Jackie Bosch, John W Eikelboom, Stuart J Connolly, Rafael Diaz, Peter Widimsky, Victor Aboyans, Marco Alings, Ajay K Kakkar, Katalin Keltai, Aldo P Maggioni , Basil S Lewis, Stefan Störk, Jun Zhu, Patricio Lopez-Jaramillo, Martin O'Donnell, Patrick J Commerford, Dragos Vinereanu, Nana Pogosova, Lars Ryden, Keith A A Fox, Deepak L Bhatt, Frank Misselwitz, John D Varigos, Thomas Vanassche, Alvaro A Avezum, Edmond Chen, Kelley Branch, Darryl P Leong, Shrikant I Bangdiwala, Robert G Hart, Salim Yusuf; on behalf of the COMPASS Investigators**

Lancet 2018;391:219-29

COMPASS Trial

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

- STUDY -

- **7470 Patients with stable peripheral or carotid disease**
- **Randomized:**
  - **ASA 100 mg daily**
  - **Rivaroxaban 2.5 mg bid + ASA 100 mg daily**

Anand S., et al.
LANCET 2018;391:219

COMPASS Trial

Rivaroxaban with or without aspirin in patients with stable peripheral or carotid artery disease: an international, randomised, double-blind, placebo-controlled trial

- Results -

- **28% reduction in stroke, MI, CV death (p = .0047)**
- **46% reduction in major adverse limb events (p = .0037)**

Significant reduction of both MACE and MALE!

Anand S., et al.
LANCET 2018;391:219

VOYAGER Trial

Rivaroxaban in Peripheral Artery Disease after Revascularization

Marc P. Bonaca, M.D., M.P.H., Rupert M. Bauersachs, M.D., Sonia S. Anand, M.D., E. Sebastian Debus, M.D., Ph.D., Mark R. Nehler, M.D., Manesh R. Patel, M.D., Fabrizio Fanelli, M.D., Warren H. Capell, M.D., Lihong Diao, M.D., Nicole Jaeger, M.S., Connie N. Hess, M.D., M.H.S., Akos F. Pap, M.Sc., John M. Kittelson, Ph.D., Ivan Gudz, M.D., Ph.D., Lajos Mátyás, M.D., Dainis K. Krievins, M.D., Rafael Diaz, M.D., Marianne Brodmann, M.D., Eva Muehlhofer, M.D., Lloyd P. Haskell, M.D., Scott D. Berkowitz, M.D., and William R. Hiatt, M.D.

NEJM 2020;382:1994-2004

VOYAGER Trial

Rivaroxaban in Peripheral Artery Disease after Revascularization

- Study -

6564 Patients having prior lower extremity revascularization……randomized……..

- **ASA 100 mg daily**
- **Riva 2.5mg bid + ASA 100 mg daily**

Bonaca M., et al
NEJM 2020;382:1994

VOYAGER Trial

Rivaroxaban in Peripheral Artery Disease after Revascularization

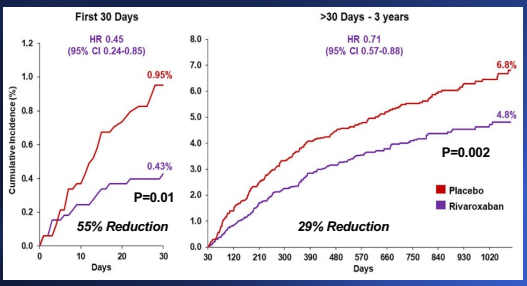
- Results -

- **15% reduction in MALE + MACE (p = .009)**
- **12% reduction in revascularizaton for recurrent limb ischemia (p = .03)**

Bonaca M., et al
NEJM 2020;382:1994

VOYAGER Trial

Effect of Rivaroxaban on acute limb ischemia after lower extremity revascularization



Hess CN et al
Circulation 2021;144:1831

Conclusions

1. *PAD is associated with a significant prothrombotic state*
2. *CLI is commonly caused by arterial thrombosis, frequently in the absence of significant plaque stenosis*
3. *Dual pathway inhibition with Rivaroxaban 2.5 mg bid + 100mg ASA OD significantly reduces MACE and MALE, and acute occlusion post LE revasc.*

Thank You