Secondary Stroke Prevention

Canadian Stroke Best Practices Update 2017

Heart and Stroke Foundation

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NIAGARA REHAB DAY 2019

LAKESHORE CARDIOLOGY

Presenter Disclosures
Dr. F. Emilio Raimondo

- No significant conflicts identified for this presentation
- Relationships with commercial interests
  Grants/research support: Pfizer, Boehringer-Ingelheim, Servier, Novartis
  Speakers Bureau/Honoraria: Pfizer, B-I, Servier, Novartis, Bayer
  Consulting Fees: Novartis, Pfizer, Boehringer-Ingelheim

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Disclosure of Commercial Support

- This program has not received financial support from any pharmaceutical company, Heart and Stroke Foundation of Canada

- Potential for Conflicts of Interest
  None for Dr. F. E. Raimondo
  no products/medications will be benefitted

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Secondary Prevention of Stroke Update 2017 (final edition)

- Wein T, Gladstone D (Writing Group Chairs) on behalf of the Canadian Stroke Best Practice Recommendations
- November 2017 Heart and Stroke Foundation
- Representative group of Neurologists, Cardiologists, Rehabilitation Medicine, Vascular surgery, Family Medicine, Dieticians, Stroke Nurse practioners across Canada

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Outline

- Focus on Secondary Prevention
- Lifestyle
- Blood Pressure
- Lipid Management
- Diabetes Management
- Antiplatelet Therapy for Ischemic Stroke and TIA
- Dual Anti-thrombotic therapy for Stroke, COMPASS study
- Anticoagulation for Stroke/TIA and Atrial Fibrillation
- Cardiac Issues in Individuals with Stroke

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Lifestyle and Risk Factor Management

- Healty Balanced Diet
  Fruits and Vegetable intake, Mediterranean Diet, reduced refined sugars, processed meats, dairy intake
- Sodium <2 gm per day
- Exercise Strenuous exercise 3-4 times per week, 150 mins+
- Weight BMI <25, waist <102 cm men, <88 cm women
- Alcohol Consumption women <10 per week, men <15 per week avoiding binges, <3 at a sitting
- Oral Contraceptives conflicting data in primary prevention, should be likely stopped in secondary prevention

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Lifestyle and Risk Factor Management

- Recreational Drug Use Cocaine, stimulants should be discontinued
- Smoking Cessation for Tobacco and other inhaled substances identify smokers, non-judgmental advice, prepare for nicotine withdrawl, offer smoking cessation program with nicotine replacement, Varenicline/Bupropion

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Blood Pressure Assessment

- Single most important modifiable risk factor in stroke needs to followed regularly in all stroke/TIA patients
- Antihypertensive therapy clearly reduces risk of stroke
- BP of over 130/85 requires further evaluation and management refer to CHEP guidelines
- Resistent hypertension need to look for secondary causes Renal, Metabolic, Sleep disorder, Alcohol, Conflicting Drugs, etc
- Aggessive lifestyle changes clearly recommended exercise, weight loss, diet, alcohol, tobacco

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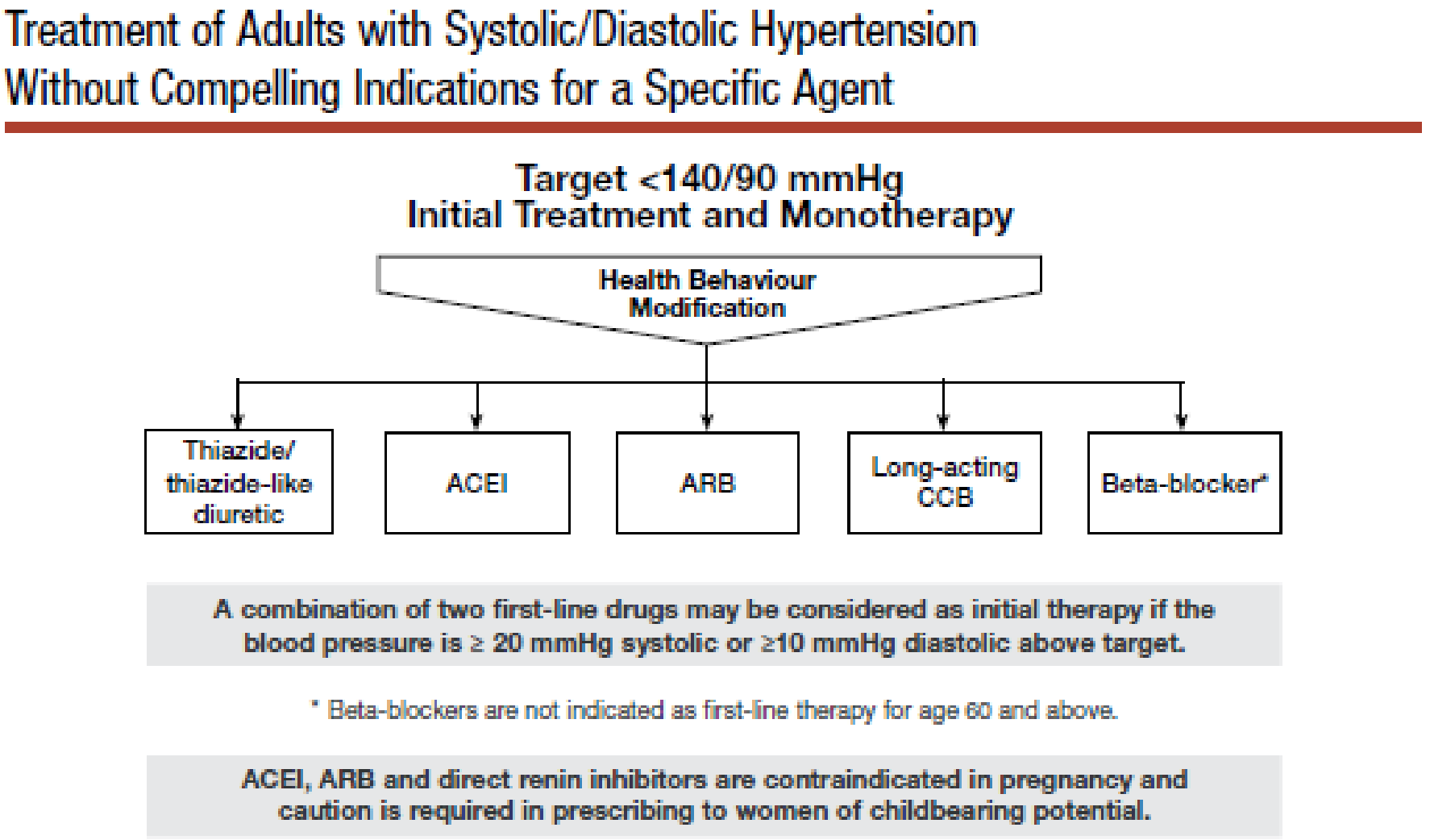
Blood Pressure Management

- In stroke/TIA patients a BP of <140/90 is recommended
- In small subcortical strokes a BP of <130 is suggested
- In Diabetics BP of <130/80
- In Chronic Kidney disease <140/90
- Timing of BP targets following stroke not clearly defined but should be initiated prior to discharge, in the hyperacute phase 0-72 hrs depends on the type, size/severity of the stroke

Figure 3.2: CHEP Treatment Algorithm 2016 (Reproduced with Permission, CHEP 2016)



Lipid Management

- Lipid levels should be assessed for all patients with stroke/TIA include LDL and HDL, total cholesterol and TG's
- Statin therapy should be first line therapy with a target goal LDL of <2.0 mmol/l or a 50% reduction in LDL from baseline
- In patients with also CAD, a target LDL of 1.8 mmol/l should be targeted
- In diabetics with ischemic stroke, high risk of recurrence and statin therapy again indicated with LDL goal of <2.0
- No advantage of statin therapy in intracerebral hemorrhage

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Lipid Management

- Fourier trial recently suggested adding a PCSK-9 inhibitor evolocumab to a statin also reduces risk of stroke bringing down LDL further to 1.45 mmol/l
  these agents would be considered in patients not at target with adequate statin dosing

Diabetes Management

- All patients should be screened for DM, A1C measured
- A1C level of <7 are target for both type 1 and 2 Diabetics with post prandial glucose levels of 5-10 mmol/l if possible
- Avoidance of hypoglycemia is important to reduce CV events
- Consideration in using SGLT-2 inhibitors, eg. empagliflozin or GLP-1 analogues eg. liraglutide have recently been shown to reduce CV events in higher risk diabetics including stroke

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Antiplatelet Therapy

- All patients with *ischemic* stroke or TIA should be prescribed an antiplatelet agent, ASA, clopidogrel, or ASA-dipyridamole are all appropriate first line agents
- Short term use of combined ASA-clopidogrel is recommended in smaller stroke in the first 21 days, modest benefit
- Longterm use of combined ASA-clopidogrel is not recommended unless other cardiac indications (stenting) because of bleeding risk
- POINT trial NEJM July 2018,in stroke/TIA benefit to DAPT but excess bleeding was seen at 90 days
- SOCRATES TRIAL ASA vs Ticagrelor no benefit
- Benefit is always offset by higher bleeding rates.

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Antiplatelet therapy Clinical Considerations

- If a patient experiences a stroke on an antiplatelet agent, switching to another eg. ASA to clopidogrel is reasonable, or to the combination ASA-dypiridamole
- All other vascular risk factors should be optimized, and consider a further search for other causes (carotid disease, atrial fibrillation)

Anticoagulation for Individuals with Stroke and Atrial Fibrillation

- An ECG is always mandatory in Stroke patients to assess for atrial fibrillation. Initial 24 hr monitoring in the acute phase is recommended assessing for atrial fibrillation
- In strokes of undetermined origin where cardioembolic cause is suggested, longterm holter monitoring over 2 weeks is suggested along with echocardiography
- 30 seconds of atrial fibrillation is the diagnostic requirement

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Anticoagulation in Patients with Atrial Fibrillation

- A direct acting oral anticoagulant(DOAC) is recommended in patients over warfarin as first line agents; consider dabigatran, apixiban, rivaroxaban, or edoxaban
  clinical circumstances need to be considered, particularly renal function
- Warfarin is already used could be continued if INR levels are easily maintained between 2-3
- Warfarin is indicated in Rheumatic valvular heart disease and in patients with Mechanical valvular prostheses
- Bridging with heparin in patients not recommended, using antiplatelet therapy should be considered as a bridge

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Atrial Fibrillation Anticoagulation Clinical Considerations

- Optimal timing for anticoagulation following stroke in atrial fibrillation has not been determined by clinical trial, decision depends on a number of clinical factors including infarct size, risk of hemorrhage
- Expert consensus has suggested initiating anticoagulation
  1 day following a TIA
  3 days following a small stroke
  6 days following a moderate stroke
  12 days following a severe stoke without hemorrhagic transformation
- In patients unable to be anticoagulated consider initially dual antiplatelet therapy or a Left atrial occluder device (Watchman)

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Anticoagulation Clinical Considerations

- drug compliance is critical in anticoagulated patients on either warfarin or DOAC's
- Monitoring of renal function in DOAC treated patients is necessary with appropriate dose adjustment.
- DOAC's are short acting medications and patients need to be advised against missing doses, cutting doses etc, as a clear increase in stroke risk exists
- Concomitant antiplatelet therapy is not recommended due to increased bleeding risk unless other clinical circumstances exist (coronary stenting)

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Publication in *New England Journal of Medi*

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

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. 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. 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

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DOI: 10.1056/NEJMoa1709118

Dual Anti-thrombotic therapy
COMPASS STUDY

- NEJM Aug 2017, Dr John Eikelboom lead investigator, McMaster
- 27,395 pts with stable CV disease, including PAD, carotid disease, recent CABG, randomized to ASA 80 mg/d alone, ASA + rivaroxaban 2.5 mg po bid, or rivaroxaban 5 mg po bid alone
- Mean follow up of 23 mos, study stopped early due to strength of the treatment outcome

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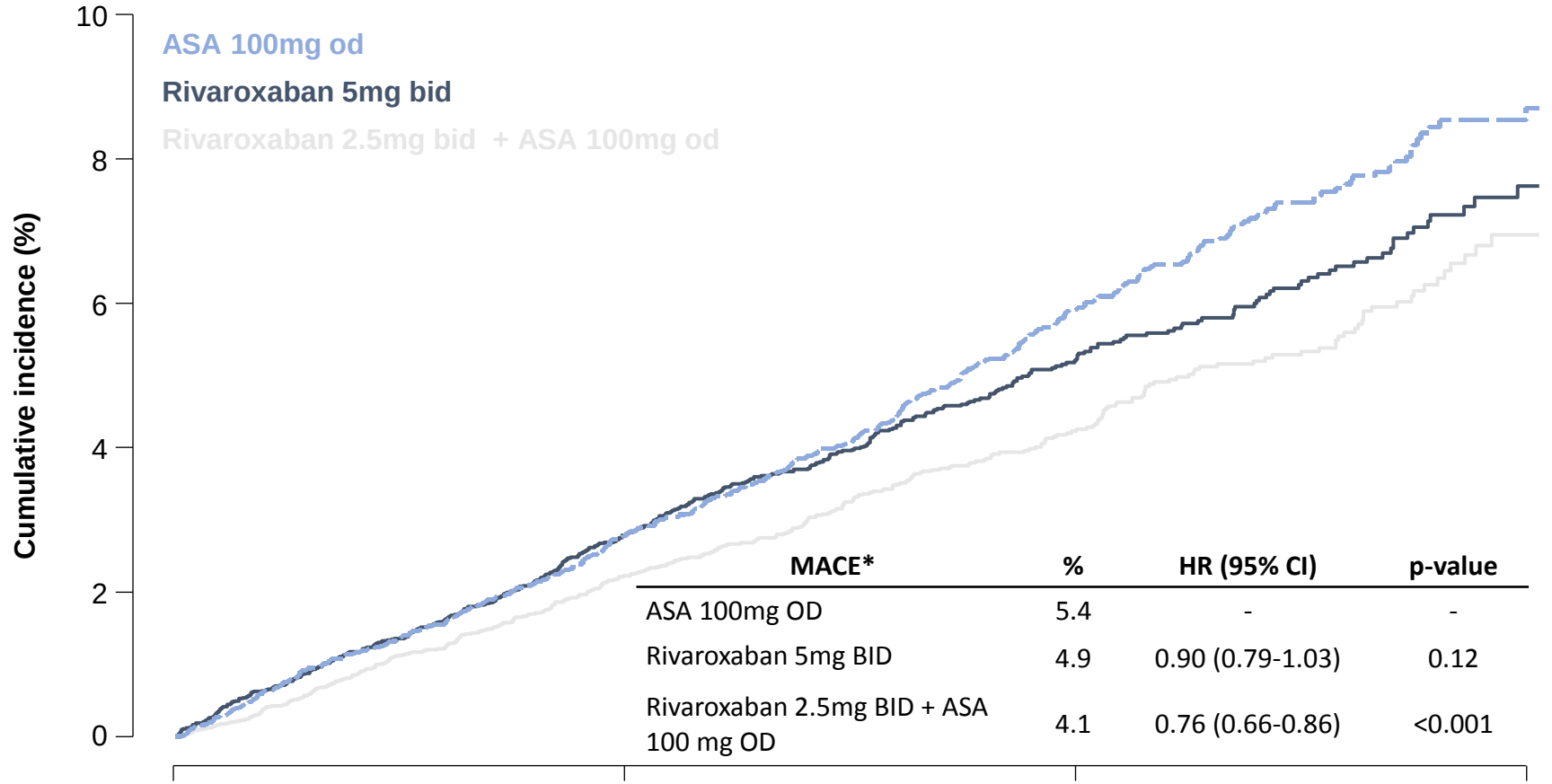
Dual Pathway Inhibition with Rivaroxaban Vascular Dose 2.5 mg bid + ASA Reduced CV Death, Stroke and MI



MACE*	%	HR (95% CI)	p-value
ASA 100mg OD	5.4	-	-
Rivaroxaban 5mg BID	4.9	0.90 (0.79-1.03)	0.12
Rivaroxaban 2.5mg BID + ASA 100 mg OD	4.1	0.76 (0.66-0.86)	<0.001

Number at risk				
ASA 100mg od	9126	7808	3860	669
Riva 5mg bid	9117	7824	3862	670
Riva 2.5mg bid + ASA 100mg od	9152	7904	3912	658

*Rates as at mean follow up of 23 months

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

Population Health Research Institute
HEALTH THROUGH KNOWLEDGE

Stroke

Event	**R + A** N=9,152	**Aspirin** N=9,126	**Rivaroxaban + aspirin vs. aspirin**	
	N (%)	**N (%)**	**HR (95% CI)**	**p**
Stroke	83 (0.9)	142 (1.6)	0.58 (0.44-0.76)	<0.0001
Ischemic	64 (0.7)	125 (1.4)	0.51 (0.38-0.69)	<0.0001
Hem Transformation	5 (<0.1)	14 (0.2)	0.35 (0.13-0.99)	0.04
Hemorrhagic	15 (0.2)	10 (0.1)	1.49 (0.67-3.31)	0.33

Sharma M, et al. Circulation 2019 available on-line

Consistent Benefit Of Rivaroxaban 2.5 mg bid + ASA Supported by Secondary Outcomes, Including All-Cause Mortality

Outcome	Rivaroxaban 2.5 mg bid + ASA 100 mg N=9152	ASA 100 mg N=9126	Rivaroxaban 2.5 mg bid + ASA 100 mg vs ASA 100 mg	
			HR (95% CI)	*p*-value*
CHD death, ischaemic stroke, MI, ALI	329 (3.6%)	450 (4.9%)	0.72 (0.63–0.83)	<0.001
CV death, ischaemic stroke, MI, ALI	389 (4.3%)	516 (5.7%)	0.74 (0.65–0.85)	<0.001
Mortality (all-cause)	313 (3.4%)	378 (4.1%)	0.82 (0.71–0.96)	0.01

*pre-specified threshold *p*=0.0025

CHD coronary heart disease death: death due to acute MI, sudden death, or CV procedure

Eikelboom JW *et al. N Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

COMPASS

The Role of Rivaroxaban in the Context of Usual Vascular Protective Therapies

RRR	Lipid lowering (1mmol/L)[1,2]	BP Lowering (10mm Hg)[3]	ACEI (HOPE)[4]	+ Riva 2.5 mg BID & ASA 100mg	COMPASS[5]
MACE	21%	20%	22%		**24%**
Stroke	15%	27%	32%		**42%**
MI	24%	17%	20%		**14%***
Death	9%	13%	16%		**18%**

*Trend towards reduction, not statistically significant

Benefits of COMPASS are on top of standard optimized control of lipids, blood pressure and RAAS blockade

1. CTT Collaboration. *Lancet 2015*;385:1397-1405; 2. Collins R, *et al. Lancet* 2016;388:2532-61. 3. Ettehad D, *et al. Lancet* 2016;387:957-67
4. HOPE Investigators. *N Engl J Med* 2000;342:145-53; 5. Eikelboom JW *et al. New Engl J Med* 2017; DOI: 10.1056/NEJMoa1709118

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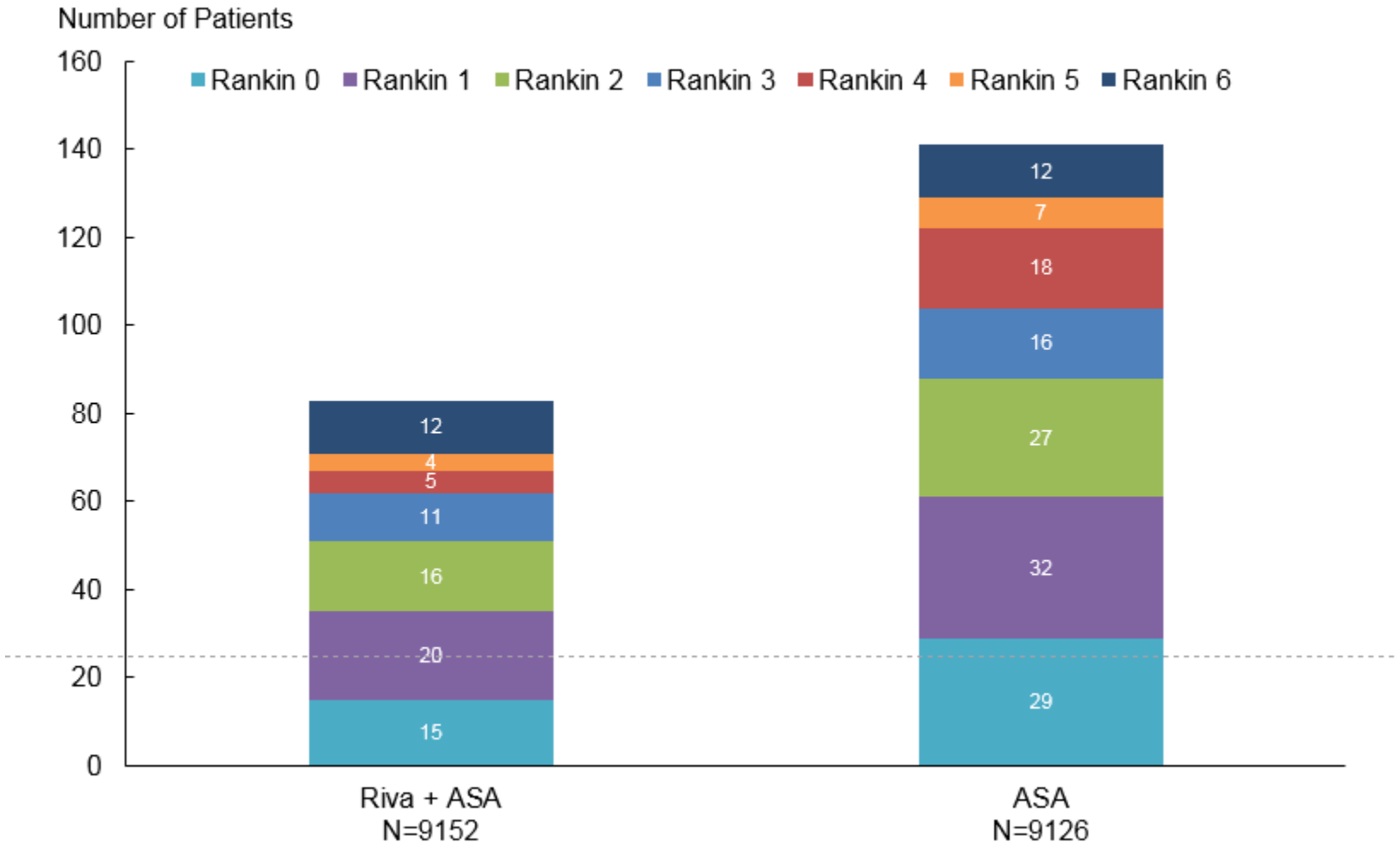
Stroke severity by modified Rankin Scale scores



Sharma M, et al. Circulation 2019 available on-line

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COMPASS in context
Proven secondary prevention therapies

	COMPASS Rivaroxaban + aspirin	Lipid lowering (1mmol/L)	BP lowering (10mm Hg)	ACE meta-analysis	SGLT2 inhibitors (Empagliflozin)	PCSK9 inhibitor (Alirocumab)
Triple outcome	**-24%**	-21%	-20%	-18%	-14%	-14%
Death	**-18%**	-9%	-13%	-14%	-32%	-15%
Stroke	**-42%**	-15%	-27%	-23%	+18%	-27%
MI	**-14%***	-24%	-17%	-18%	-13%	-12%

*Not significant

Eikelboom J, et al. N Engl J Med 2017; 377: 1319-1330. Ettehad D, et al. Lancet 2016;387:957-67. CTT Collaboration. Lancet 2015;385:1397-1405; Collins R, et al. Lancet 2016;388:2532-61. Dagenais GR, et al. Lancet. 2006; 368:581-8. Schwartz GG, et al. N Engl J Med 2018;379:2097-2107. Zinman B, et al. N Engl J Med 2015; 373: 2117-2128.

Cardiac Issues in Patients with Stroke

- **PFO** new guidelines 2017
  in patients with cryptogenic stroke between ages of 18-60 yrs, a PFO closure with antiplatelet therapy is now recommended over anticoagulation
  in patients already on anticoagulation, the decision to close a PFO is unclear as little data exists and further decisions based on individual factors

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Cardiac Issues in Patients with Stroke

- Aortic Arch atheroma
  often difficult to diagnose, no other identified cause for the recurrent stroke, no convincing beneficial therapy of antiplatelet therapy over anticoagulant therapy
  consider optimizing all other risk factors
- Heart Failure with reduced EF, and a mural thrombus, anticoagulation with Warfarin for 3 months at least
  in patients without detected thrombus, and poor EF, decision to anticoagulate or use antiplatelet therapy is individualized.

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Summary

- A team approach to treating stroke victims is of utmost importance
- Prevention of further stroke is very successful, with particular emphasis on treating risk factors, managing blood pressure, and antithrombotic therapy

Questions?

Thank you

Dr. Emilio Raimondo

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