Bale/Doneen Live Chat Session

1/8/2014

5:30-6:30 pm PST

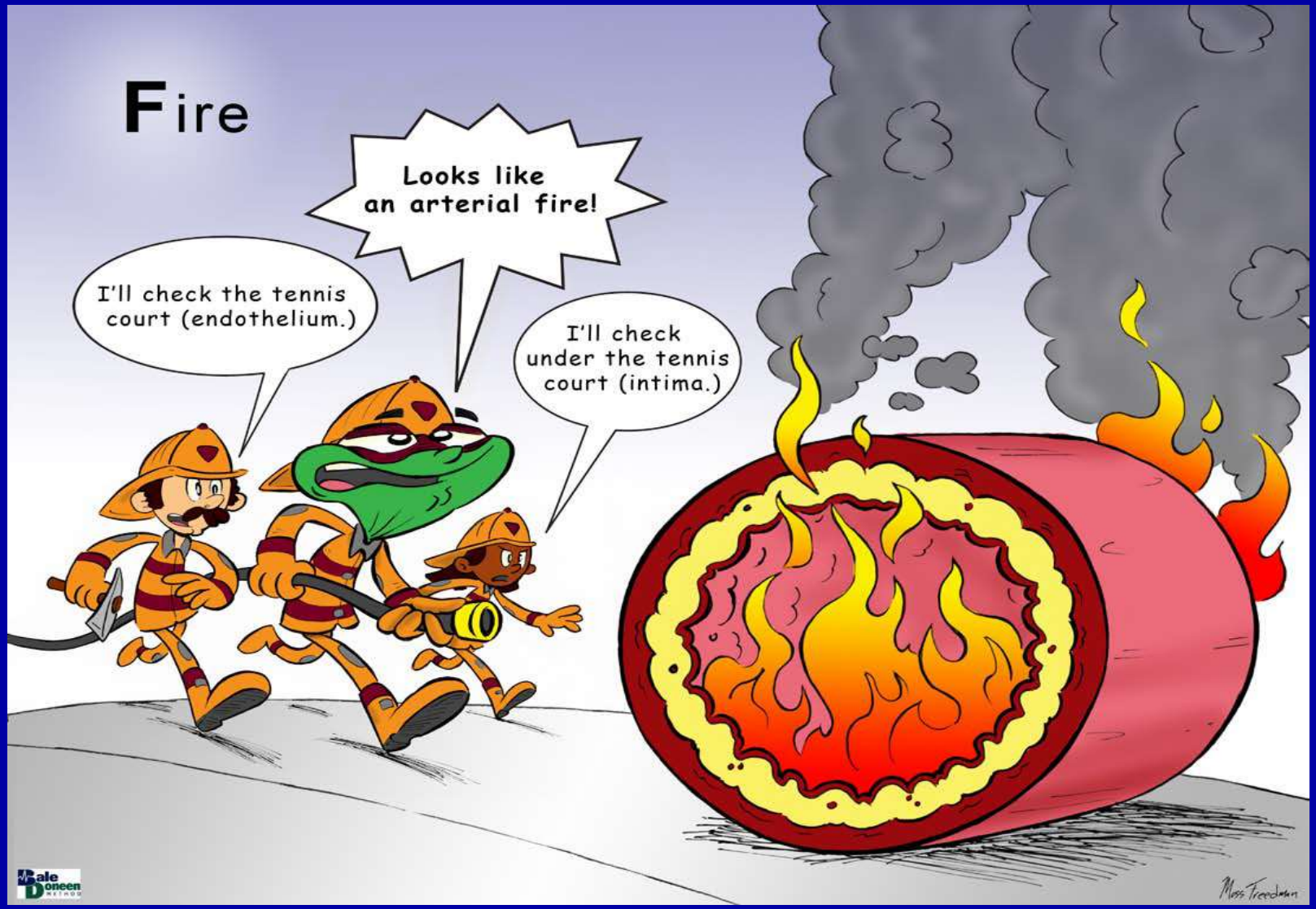
Bradley Bale, MD

Outline

- New data and slides
- Case study
- Review upcoming meetings
- Open discussion for remaining

New Studies: Lots to Choose

Inflammation



Low Bilirubin Associated with Silent Stroke Risk

- 2,865 pts; 36% female; age range 30-69 yo; presented for PE; all received MRI of brain; 343 had evidence of silent stroke (SS).
- Subjects with SS had lower total bilirubin and also: higher BMI, BP, TC, TG, LDL, BS; lower GFR, HDL.
- SS pts. were older, more likely male & smokers, higher alcohol intake.

Li, R.-Y., et. al. (2013). Decreased Serum Bilirubin Is Associated With Silent Cerebral Infarction. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.303003

Low Bilirubin Associated with Silent Stroke Risk

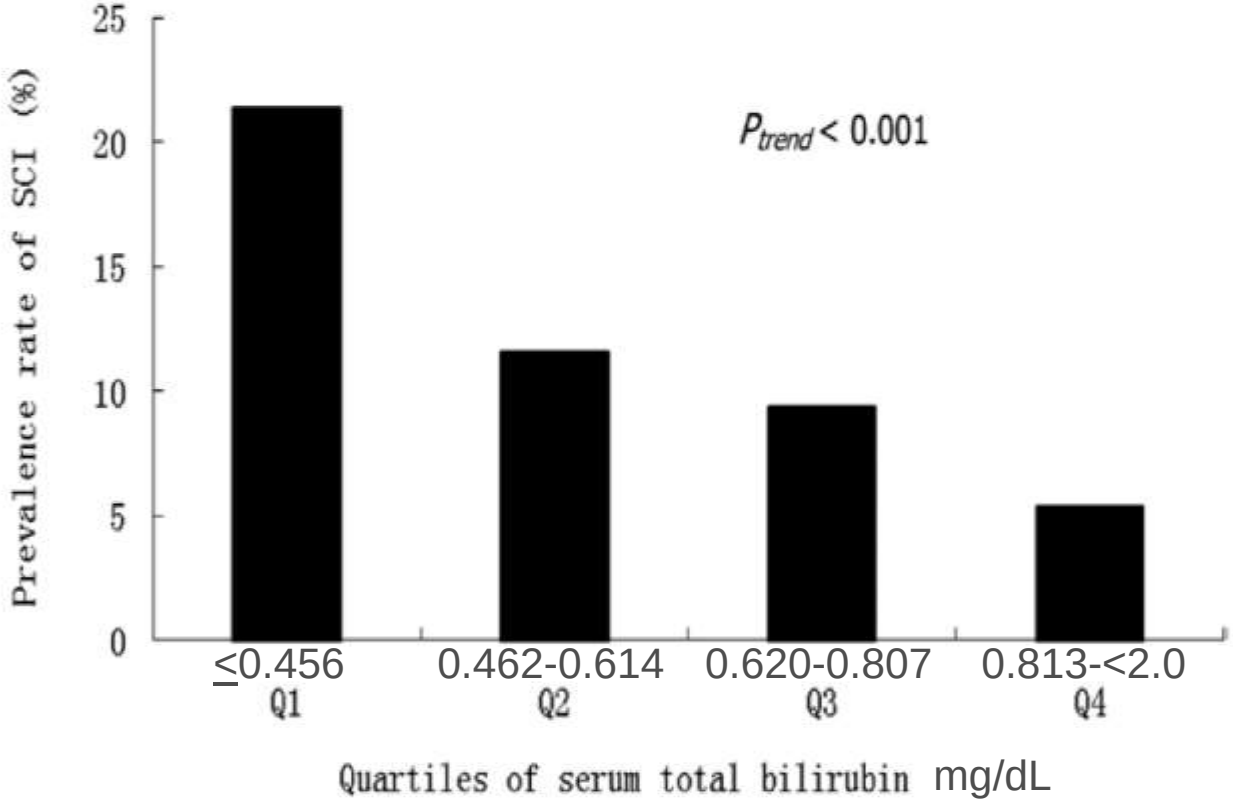


Figure. The association between serum total bilirubin levels and prevalence rate of silent cerebral infarction (SCI; %). Participants were stratified into quartiles according to their total bilirubin levels.

Li, R.-Y., et. al. (2013). *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.303003

Low Bilirubin Associated with Silent Stroke Risk

Table 3. Adjusted ORs and 95% CIs for the Presence of SCI, Based on Logistic Regression With Backward Stepwise Selection

Variables	β	OR (95% CI)	*P* Value
Sex (male/female)	0.956	2.600 (1.772–3.816)	<0.001
BMI, kg/m²	0.046	1.047 (1.001–1.096)	0.047
Smoking (yes/no)	0.476	1.610 (1.172–2.212)	0.003
DBP, mm Hg	0.039	1.039 (1.019–1.060)	<0.001
baPWV, cm/s	0.006	1.006 (1.005–1.007)	<0.001
TB, μmol/L	−0.078	0.925 (0.897–0.954)	<0.001
LDL-C, mmol/L	0.269	1.309 (1.106–1.550)	0.002
FPG, mmol/L	0.434	1.543 (1.230–1.934)	<0.001
eGFR, mL/min per 1.73 m²	−0.034	0.967 (0.958–0.976)	<0.001
DM (yes/no)	0.712	2.037 (1.169–3.551)	0.012

Adjusted ORs were derived from the final logistic regression model which includes all significant factors. baPWV indicates brachial-ankle pulse wave velocity; BMI, body mass index; CI, confidence interval; DBP, diastolic blood pressure; DM, type 2 diabetes mellitus; eGFR, estimated glomerular filtration rate; FPG, fasting plasma glucose; LDL-C, low-density lipoprotein cholesterol; OR, odds ratio; SCI, silent cerebral infarction; TB, total bilirubin; and β, partial regression coefficient.

Adjusted for 21 conventional risk factors

TB was an independent risk factor of SS.

Risk on par with BMI, DBP, GFR

Li, R.-Y., et. al. (2013). *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.303003

Low Bilirubin Associated with Silent Stroke Risk

- TB is a novel biochemical indicator for SS regardless of classical CV risk factors.

- Early measurement of TB may be useful to assess the risk of SS.

Li, R.-Y., et. al. (2013). Decreased Serum Bilirubin Is Associated With Silent Cerebral Infarction. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.303003

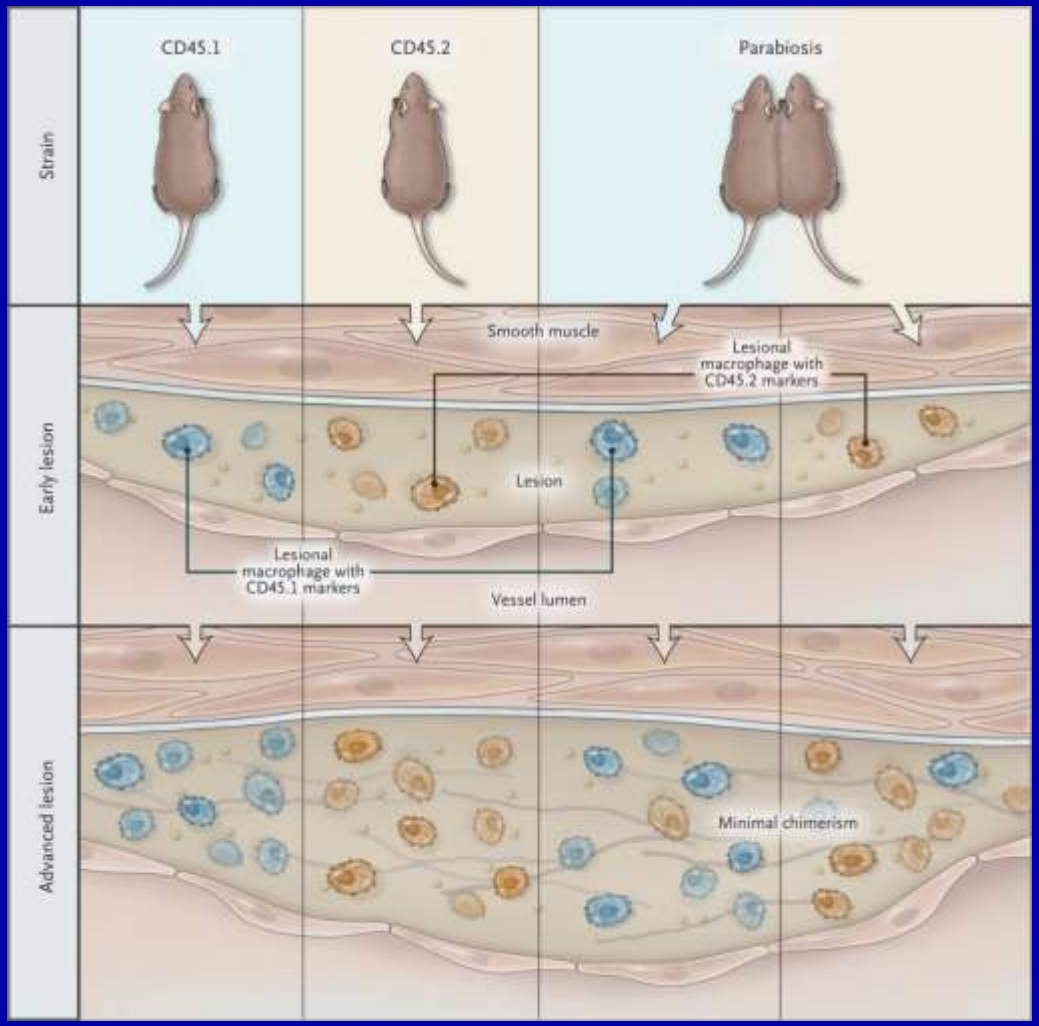
BDM Thoughts

- Study supports previous evidence regarding TB as a powerful endogenous anti-inflammatory agent.
- Clinically, we need to monitor the level and seek out healthy ways (i.e. exercise) to increase bilirubin when it is low.
- Target should be at least 0.6 mg/dL

What??

Al Lopez alerted us to this – thanks, Al !

Macrophages can Proliferate in an Atheroma



Robbins et al.1 used parabiosis, the tethering of the circulatory systems of two mice (one in which the monocytes expressed the cell-surface marker CD45.1, and the other in which the monocytes expressed the cell-surface marker CD45.2), to test whether lesional macrophages mirror the chimerism of monocytes present in the combined circulatory system or whether they originate from the host mouse. Robbins et al. found that the lesional macrophages originated predominantly from the host mouse, and they concluded that the proliferation of macrophages within the atherosclerotic lesion is a driver of lesion progression

Chimerism- manifestation of two sets of DNA; not present in atheromas

Parks BW, Lusis AJ. N Engl J Med 2013;369:2352-2353.

1. Robbins, C. S., et. al. (2013). Local proliferation dominates lesional macrophage accumulation in atherosclerosis. *Nat Med, 19*(9), 1166-1172.

BDM Thoughts

- Need an experiment in humans to confirm this can happen.
- If it can, it will be interesting to know what are the triggers.
- This would mitigate to some degree the importance of MCP.

Inhibition of NF-κB by miRNA-181b Reduces Arterial Inflammation and ASVD

- ASVD is a chronic inflammatory condition.
- Nuclear factor-κB (NF-κB)–activation plays a critical role in initiating and propagating arterial inflammation.
- The transcriptional activity of NF-κB can be induced by a variety of stimuli: inflammatory cytokines, Ox-LDL, LPS, FFA, etc. (remember innate immune syst. TLRs)

Sun, X., et. al. (2014). Systemic Delivery of MicroRNA-181b Inhibits NF-kappaB Activation, Vascular Inflammation, and Atherosclerosis in Apoe-/- Mice. *Circ Res*. 114 (1):32-40

Inhibition of NF-κB by miRNA-181b Reduces Arterial Inflammation and ASVD

- MicroRNAs (miRs) are single-stranded, noncoding, small RNAs that regulate gene expression by destabilizing target mRNAs or inhibiting translation.

- miR-181b inhibits endothelial NF-κB derived inflammation by reducing the expression of importin-α3 (IPOA3), a protein critical for NF-κB translocation from cytoplasm to nucleus.

Sun, X., et. al. (2014). Systemic Delivery of MicroRNA-181b Inhibits NF-kappaB Activation, Vascular Inflammation, and Atherosclerosis in Apoe-/- Mice. *Circ Res*. 114 (1):32-40

Inhibition of NF-κB by miRNA-181b Reduces Arterial Inflammation and ASVD

- Investigated the role of miR-181b in the development of atherosclerosis in ApoE−/− mice.

- Mice fed HFD for 12 wks that received systemic miR-181b had ~ 44% less ASVD in aorta & ~ 25% less lesion size.

Sun, X., et. al. (2014). Systemic Delivery of MicroRNA-181b Inhibits NF-kappaB Activation, Vascular Inflammation, and Atherosclerosis in Apoe-/- Mice. *Circ Res*. 114 (1):32-40

Inhibition of NF-κB by miRNA-181b Reduces Arterial Inflammation and ASVD

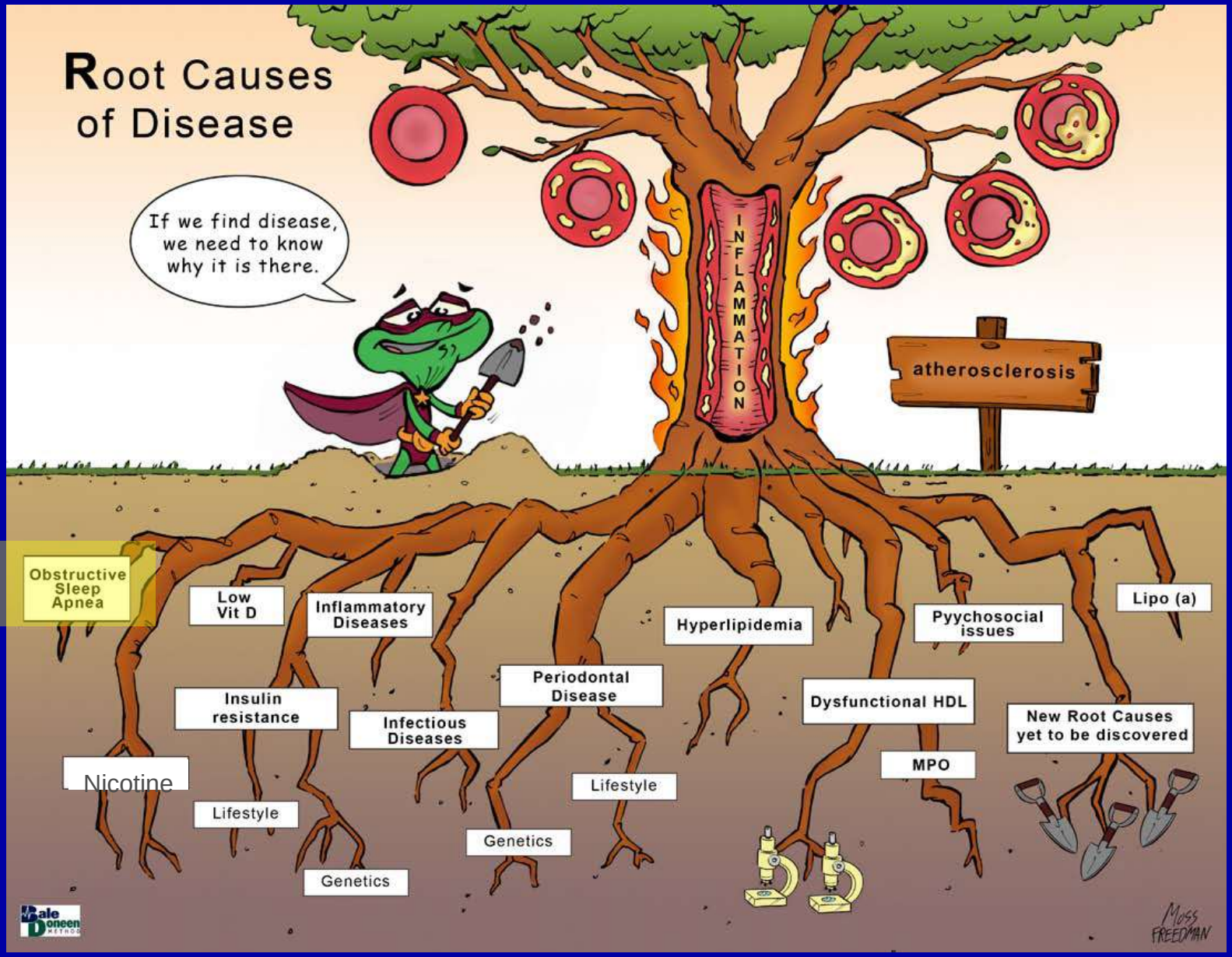
- Findings revealed cell-specific mechanisms (IPOA3) by which miR-181b inhibits NF-kB translocation to nucleus.

- Provides rationale for the potential clinical use of miR-181b mimetics to treat chronic vascular inflammatory diseases such as atherosclerosis.

Sun, X., et. al. (2014). Systemic Delivery of MicroRNA-181b Inhibits NF-kappaB Activation, Vascular Inflammation, and Atherosclerosis in Apoe-/- Mice. *Circ Res*. 114 (1):32-40

BDM Thoughts

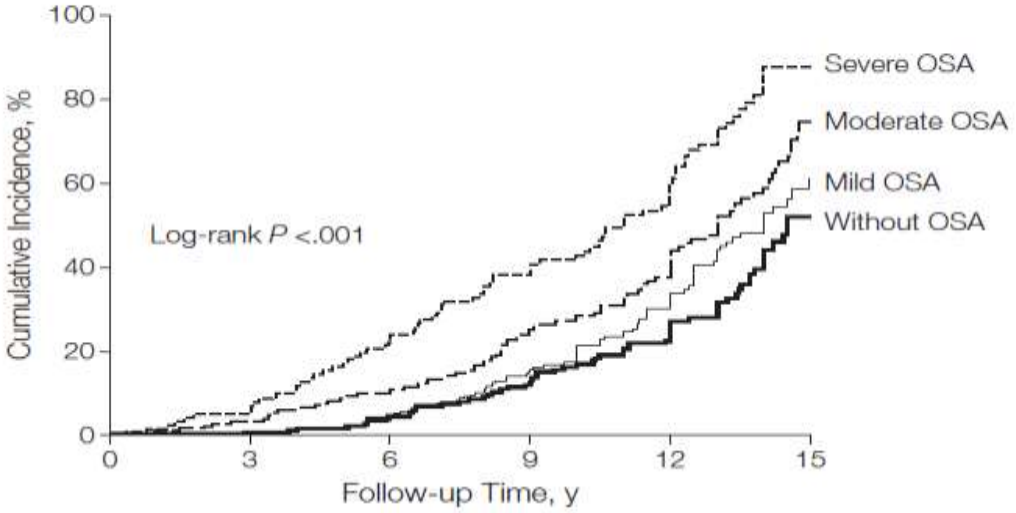
- Study supports inflammation as causal
- Study supports importance of NF-kB
- Makes more sense to mitigate the stimuli for NF-kB such as, LPS (PD), FFA (diet), Ox-LDL (lipid rx), inflam. cytokines (IR, psycho-social and sleep), aging (autophagy – premature senescence), than to develop miR treatments.



Recent Review of OSA and Hypertension

OSA and Hypertension: OSA increases risk of developing BP

Figure 2. Cumulative Incidence of Hypertension in Participants Without OSA and Untreated Patients With OSA



No. at risk						
Severe OSA	199	184	141	119	62	37
Moderate OSA	258	222	202	162	114	67
Mild OSA	298	289	260	194	127	59
Without OSA	310	306	269	211	152	72

OSA indicates obstructive sleep apnea. Severity of OSA was defined by the apnea-hypopnea index (AHI) as mild OSA (AHI, 5.0-14.9), moderate OSA (AHI, 15.0-29.9), and severe OSA (AHI, ≥30.0). *P* value reflects an overall log-rank χ^2_3 test, providing an overall survival difference among the 4 study groups.

1,065 pts
followed
15 years

Konecny, T., Kara, T., & Somers, V. K. (2013). Obstructive Sleep Apnea and Hypertension: An Update. *Hypertension*. doi: 10.1161/hypertensionaha.113.00613

OSA and Hypertension: OSA most common cause of resistant BP

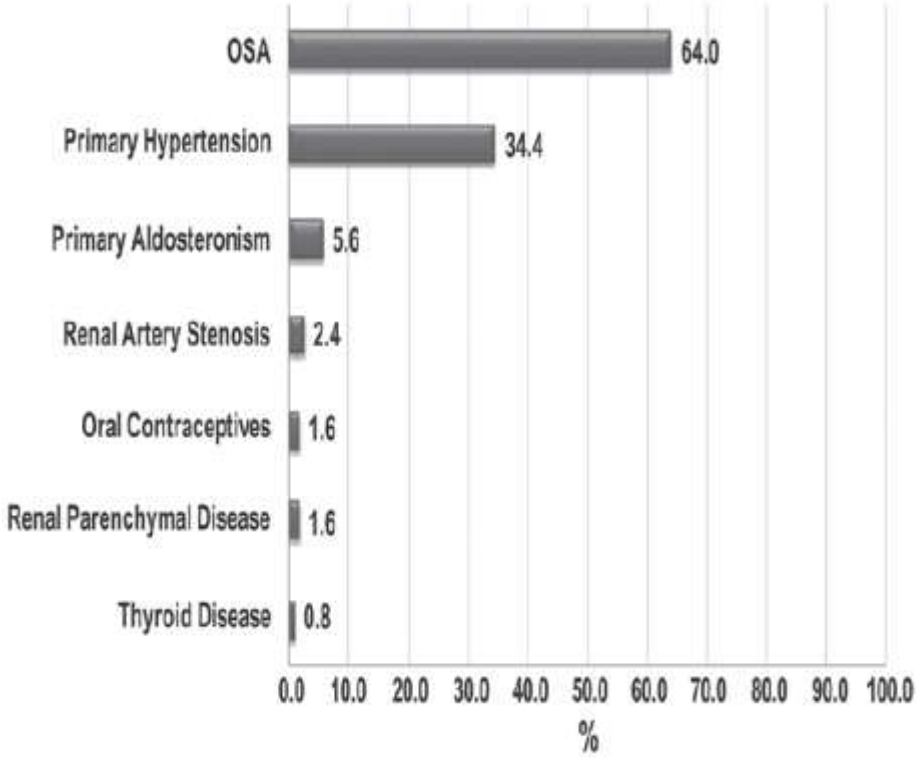


Figure 1. Prevalence of secondary causes of hypertension associated with resistant hypertension in a cohort of 125 patients from Brazil. OSA indicates obstructive sleep apnea. Reproduced from Pedrosa et al[1] with permission of the publisher. Copyright © 2011, American Heart Association, Inc.

Konecny, T., Kara, T., & Somers, V. K. (2013). Obstructive Sleep Apnea and Hypertension: An Update. *Hypertension*. doi: 10.1161/hypertensionaha.113.00613

OSA and Hypertension: CPAP treatment lowers BP in hypertensives

- Meta-analysis of 28 studies; 1,948 pts.; by Montesi et al 2012

- Found mean decrease in systolic and diastolic BP of 2.58 and 2.01 mm Hg, respectively, favoring those treated with CPAP.

Konecny, T., Kara, T., & Somers, V. K. (2013). Obstructive Sleep Apnea and Hypertension: An Update. *Hypertension*. doi: 10.1161/hypertensionaha.113.00613

OSA and Hypertension: CPAP rx effective for prehypertension and masked BP

- 36 males with severe OSA and prehypertension or masked hypertension (24 hr. BPM)
- Randomized to 3 mos. CPAP rx or no rx
- CPAP reduced frequency of prehypertension from 94% to 55%-P=0.02 and masked hypertension from 39% to 5%-P=0.04; no change – no rx

Konecny, T., Kara, T., & Somers, V. K. (2013). Obstructive Sleep Apnea and Hypertension: An Update. *Hypertension*. doi: 10.1161/hypertensionaha.113.00613

OSA and Hypertension: alternative rx to CPAP

- Oral appliances offer an important and effective alternative in mild to moderate OSA.
- Weight loss
- No mention of Provent

Konecny, T., Kara, T., & Somers, V. K. (2013). Obstructive Sleep Apnea and Hypertension: An Update. *Hypertension*. doi: 10.1161/hypertensionaha.113.00613

OSA and Hypertension

OSA is a modifiable and highly prevalent factor in the development of HTN.

Konecny, T., Kara, T., & Somers, V. K. (2013). Obstructive Sleep Apnea and Hypertension: An Update. *Hypertension*. doi: 10.1161/hypertensionaha.113.00613

BDM Thoughts

- Always keep OSA on radar screen
- Pts with resistive hypertension should get a formal sleep study regardless of history

How to Treat Chronic Periodontits??

Study provided by Thomas Nabors, DDS; thanks, Tom!

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

- 101 PD pts; double blinded RCT; rx scaling & root planning (SRP)-only or with metronidazole (MTZ) 400 mg/TID or MTZ+AMX (500 mg/TID) for 14 days; half of each group rinsed with 0.12% chlorhexidine (CHX) BID for 2 mos.

- Nine subgingival plaque samples/pt analyzed for 40 bacterial pathogens by DNA at baseline, 3, 6 and 12 mos.

Soares, G. M. S., et. al. (2013). Metronidazole alone or with amoxicillin as adjuncts to nonsurgical treatment of Chronic Periodontitis: a secondary analysis of microbiological results from a randomized clinical trial. *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

- Pts with untreated generalized chronic PD from Periodontal Clinic in Brazil

- ≥30 yo; ≥6 teeth with PD and clinical attachment level (CAL) ≥5 mm, as well as ≥30% of the sites with bleeding on probing (BOP).

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

- 3 samples from each of the following: shallow (PD <3 mm), intermediate (PD 4–6 mm) and deep (PD >7 mm).

- Primary outcome: effects of rx on the red complex species (*T.f., T.d., P.g.*) at end of 1 year.

- Secondary outcome: effects of rx on the remaining 40 species at end of 1 year.

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

- Antibiotic-rx groups had significantly lower mean counts of key PD pathogens (red complex plus Actinomyces israelli, Streptococcus oralis, Capnocytophaga gracilis, E. nodatum, Fusobacterium nucleatum ssp. vincentii and P. intermedia) compared to SRP group ($p<0.05$).

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

- The systemic antibiotic regimens had similar effects in the microbiota of shallow and deep sites.

- This is good because periodontal pathogens can be present in high levels even in shallow gingival crevices (SRP generally not administered in these areas).

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

- Shallow sites in MTZ+AMX group rinsed with CHX had significantly lower levels of red complex species.

- This group also had significantly higher levels of Actinomyces (healthy species which is part of the core microbiome in healthy subjects).

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

At 12 mos. post-rx, the antibiotic-rx groups exhibited a microbial profile more compatible with periodontal health than the control group.

In the SRP

group there was a clear trend for the regrowth of several species, including all members

of the red complex.

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

- Antibiotic rx groups had greater reductions in number of sites with PD ≥5 mm $p<0.05$
- There was a steady increase in the mean number of deep pockets in the SRP group.

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

Chronic Periodontitis Improved with Adjunct Antibiotic Therapy

Pts with chronic periodontitis receiving SRP benefit from adjunct rx with MTZ or MTZ+AMX

Adding CHX to SRP & MTZ+AMX has additional benefit for subgingival microbiota in shallow sites

Soares, G. M. S., et. al. (2013). *J Clin Periodontol*, n/a-n/a. doi: 10.1111/jcpe.12217

BDM Thoughts

- We defer treatment decisions of PD to the dental experts.
- This study seems to support utilization of antibiotics along with SRP in patients who have PD caused by high risk pathogens.
- Study seems to support using 0.12% CHX rinse BID for 2 mos in PD caused by high risk pathogens.

EDFROG IRA

Education	Genetics	Individual Management
Disease	Optimal	Risk factor response
Fire	Roots	Assess Disease Annually

Platelets Play a Role in the Atherosclerosis Process

- OxLDL stimulates platelets to from complexes with monocytes---platelet–monocyte aggregates (PMAs).
- At low to moderate concentrations of OxLDL, platelets double the uptake of OxLDL by monocytes.
- Platelets enhance monocyte transmigration across the endothelium and foam cell formation in response to OxLDL.

Badrnya, S., et. al. (2013). Platelets Mediate Oxidized Low-Density Lipoprotein–Induced Monocyte Extravasation and Foam Cell Formation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302919

Platelets Play a Role in the Atherosclerosis Process

- Aspirin, *in vitro*, mitigated the formation of PMAs.
- Aspirin decreased the uptake of OxLDL by monocytes in whole blood.
- P2Y12 inhibitors had similar effects.

Badrnya, S., et. al. (2013). Platelets Mediate Oxidized Low-Density Lipoprotein–Induced Monocyte Extravasation and Foam Cell Formation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302919

Platelets Play a Role in the Atherosclerosis Process

- Platelets are crucial players in the onset of atherosclerosis by facilitating leukocyte transmigration.

- Platelet-induced lipid accumulation in monocytes provide a novel mechanism for how platelets contribute to the onset and progression of atherosclerosis and negatively regulate plaque stability.

Badrnya, S., et. al. (2013). Platelets Mediate Oxidized Low-Density Lipoprotein–Induced Monocyte Extravasation and Foam Cell Formation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302919

BDM Thoughts

Anti-platelet therapy benefits may extend beyond the reduction in thrombotic risk!

Badrnya, S., et. al. (2013). Platelets Mediate Oxidized Low-Density Lipoprotein–Induced Monocyte Extravasation and Foam Cell Formation. *Arteriosclerosis, Thrombosis, and Vascular Biology*. doi: 10.1161/atvbaha.113.302919

Antiplatelet Therapy During Surgeries in CAD Patients

Treatment strategies balancing the safety and efficacy of continuing or not continuing antithrombotic medications for surgery are needed.

1,358 consecutive DES pts discharged on ASA and clopidogrel; surgery was second most common cause (major bleeding #1; dental #4) of discontinuation within 1 yr (21%) and the first cause thereafter (49%).

Capodanno, D., & Angiolillo, D. J. (2013). Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

- Antiplatelet therapy is a cornerstone in the management of pts with CAD regardless of stents.

- Discontinuing ASA therapy is estimated to potentially triple the risk of an event in tertiary prevention patients or those post CABG.

- In-'stent' thrombosis is frequently fatal or (at minimum) can result in a large STE-MI.

Capodanno, D., & Angiolillo, D. J. (2013). Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

- Surgery presents an inherently dangerous situation with an increased prothrombotic and inflammatory environment.

- Guidelines recommend delaying surgery 4 to 6 weeks after BMS placement.

- Incidence of 30-day post surgical ischemic events in pts with BMS was:
  - 2.6% when major surgery was > 45 days post BMS
  - 6.7% when the interval was <45 days post BMS

Capodanno, D., & Angiolillo, D. J. (2013). Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

- 206 pts who received ≥1 DES and underwent major non-cardiac surgery at a median of 6 mos after PCI.

- **Risk of cardiac death, MI, or stent thrombosis was increased 27-fold in the week following surgery! ***

- Unfortunately unknown how antiplatelet rx handled

*JACC Cardiovasc Interv. 2010;3:920–927.
Capodanno, D., & Angiolillo, D. J. (2013). *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

- 905 DES pts. who had surgery <45 days after stent had 30-day post surgery incidence of adverse ischemic of 20%.

  (6.7% when the interval was <45 days post BMS)

- The event rate was only 1.2% once the interval exceeded 180 days.

- Guidelines recommend: **No elective noncardiac surgeries for at least 12 mos after DES, if antiplatelet treatment to be discontinued.**

Capodanno, D., & Angiolillo, D. J. (2013). *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

- Antiplatelet agents that irreversibly inhibit platelet function, requiring 7 to 10 days for an entire platelet pool to be replaced (regardless of their half-lives):

  ASA, ticlopidine, clopidogrel, and prasugrel.

- Antiplatelet agents that reversibly inhibit platelet function:

  Dipyridamole (~10 hrs.), Cilostazol (~10 hrs.), NSAIDs (~2 to 20 hrs.), Ticagrelor (~8 to 12 hrs)

Capodanno, D., & Angiolillo, D. J. (2013). *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

Table 1. Interventions at High Bleeding Risk in Multiple Surgical and Invasive Scenarios

Type of surgery	
Cardiac surgery	Reintervention, endocarditis, coronary artery bypass grafting after failed percutaneous coronary intervention, aortic dissection
General surgery	Hepatic resection, pancreaticoduodenectomy
Maxillofacial surgery	Radical and reconstructive surgery for cancer of the head and neck, open reduction of orbital-zygomatic fracture, submandibular sialoadenectomy
Plastic surgery	Functional treatment of trauma outcomes, treatment of conspicuous postdemolitive loss of substance, large liposuction, surgical treatment of burns >15%, treatment of leg ulcers (American Society of Anesthesiology class III–IV), large lipofilling, postbariatric surgery
Thoracic surgery	Esophagectomy, pleuropneumectomy, pulmonary decortication
Vascular surgery	Open surgery of the thoracic and thoracoabdominal aorta
Digestive endoscopy	Dilation for achalasia, mucosectomy, submucosal resection, fine-needle aspiration biopsy of pancreatic cystic lesions, Vater ampulla ampullectomy
Gynecological surgery	Laparoscopic or laparotomic hysterectomy for large uterus, laparoscopic or laparotomic myomectomy, laparoscopic or laparotomic surgery for severe/deep endometriosis, debulking of ovarian cancer, radical surgery for carcinoma of the cervix and endometrium, pelvic/lombo-aortic lymphadenectomy, pelvic evisceration
Neurosurgery	Removal of intradural lesions (intracerebral masses, intraparenchymal hemorrhages)
Pneumology	Transbronchial and lung biopsies, operative bronchoscopy with a rigid bronchoscope
Dentistry	None
Ophthalmology	None
Orthopedic surgery	Major prosthetic surgery (hip, knee), major traumatology (pelvis, long bones), fractures of the proximal femur in elderly patients
Urology	Total and partial nephrectomy, percutaneous nephrostomy, percutaneous lithotripsy, radical cystectomy and prostatectomy, prostatic endoscopic resection, endoscopic bladder interventions, penectomy, partial orchiectomy

Adapted from Rossini et al[42] with permission of the publisher. Copyright © 2012, Il Pensiero Scientifico Editore. Authorization for this adaptation has been obtained both from the owner of the copyright in the original work and from the owner of copyright in the translation or adaptation.

Circulation, 128(25), 2785-2798.

Antiplatelet Therapy During Surgeries

RECOMMENDATIONS:

1. Stented patients undergoing procedures that mandate discontinuation of P2Y12 receptor inhibitors, if possible, aspirin should be continued. P2Y12 receptor should be restarted as soon as possible after the procedure.

2. DES patients who require noncardiac surgery <6 months post stent - should continue DAPT.

Circulation, 128(25), 2785-2798.

Antiplatelet Therapy During Surgeries

RECOMMENDATIONS CONT:

3. DES pts > 6 mos post stent may need to be maintained on DAPT due to high risk from any of the following:

long stented segments	left main
multiple stenting	last remaining vessel
overlapping stents	recent ACS
small vessels	history of stent thrombosis
bifurcation lesions	impaired LVEF, CKD or DM

Circulation, 128(25), 2785-2798.

Antiplatelet Therapy During Surgeries

- In high risk patients whose surgery is critical, bridging agents with rapid antiplatelet onset and offset can be utilized.

- These are the small-molecule intravenous glycoprotein IIb/IIIa antagonists (eg, tirofiban, eptifibatide).

- Main limitation: several days of hospitalization.

Capodanno, D., & Angiolillo, D. J. (2013). Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

Table 2. Key Pharmacokinetic and Pharmacodynamic Characteristics of Cangrelor and Small-Molecule Glycoprotein IIb/IIIa Antagonists

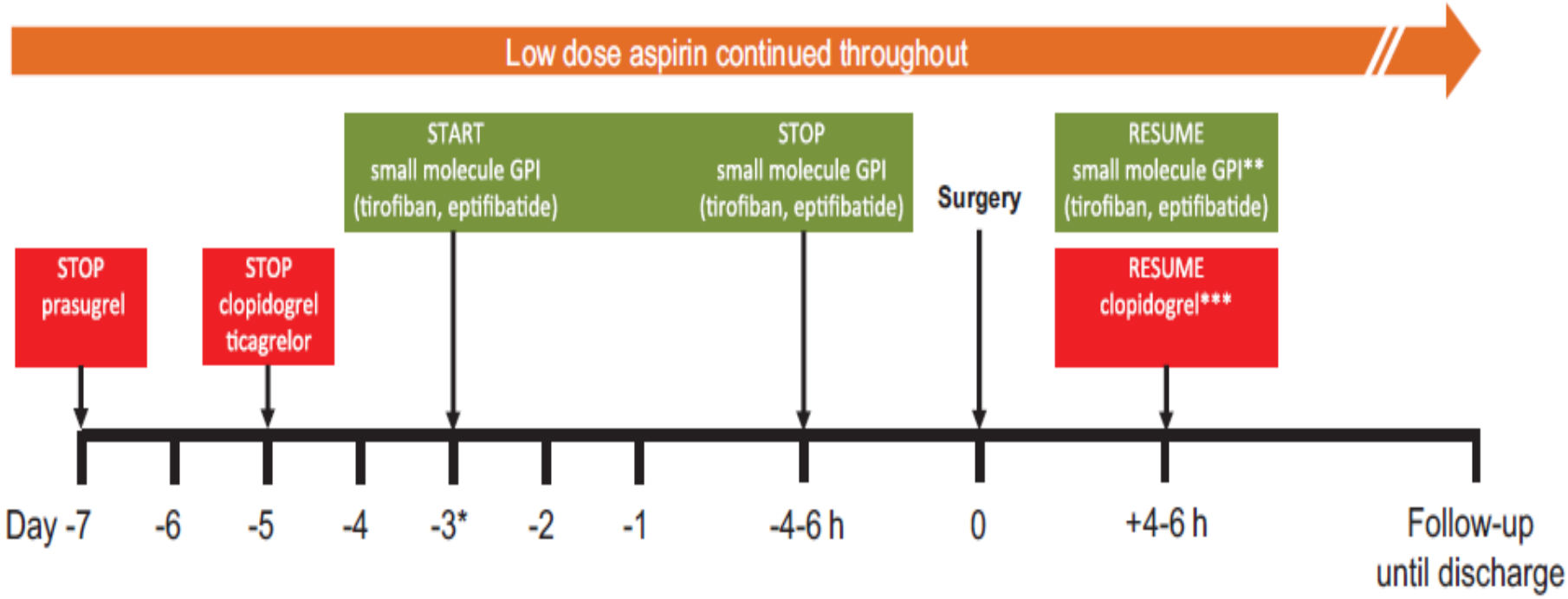
Not FDA approved

	Cangrelor	Tirofiban	Eptifibatide
Onset of action	Immediate	Immediate	Immediate
Potent platelet inhibition	Yes	Yes	Yes
Plasma half-life	3–5 min	2 h	2.5 h
Offset of action	1 h	4–8 h	4–6 h
$P2Y_{12}$-specific (natural bridge)	Yes	No	No
"Targeted" Inhibition (thienopyridine-like)	Yes	No	No

Capodanno, D., & Angiolillo, D. J. (2013). Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

Bridging strategy with small-molecule glycoprotein IIb/IIa inhibitors (GPI)



*Tirofiban: 0.1 mcg/Kg/min; If creatinine clearance <50 mL/min, adjust to 0.05 mcg/Kg/min. Eptifibatide: 2.0 mcg/Kg/min; If creatinine clearance is <50 mL/min, adjust to 1.0 mcg/Kg/min.

**If oral administration not possible

***With 300-600 mg loading dose, as soon as oral administration possible. Prasugrel or ticagrelor discouraged

Capodanno, D., & Angiolillo, D. J. (2013). *Circulation, 128*(25), 2785-2798.

Antiplatelet Therapy During Surgeries

Summary of Antiplatelet use in CAD requiring surgery:

1. Discontinuing aspirin can triple risk of an event
2. Stent thrombosis is often fatal
3. BMS Post surgery ischemic event < 45 days – 6.7%
4. DES Post surgery ischemic event < 45 days – 20%
5. Continue Aspirin in elective surgeries if possible- should be able to in any dental or ophthalmology surgery.
6. Restart P2Y12 receptor as soon as possible post surgery
7. In Surgical Patients – Consider BMS over DES due to more rapid endothelialization and shorter need for DAPT.

Capodanno, D., & Angiolillo, D. J. (2013). Management of antiplatelet therapy in patients with coronary artery disease requiring cardiac and noncardiac surgery. *Circulation, 128*(25), 2785-2798.

Bale/Doneen Take-Away

1. For surgical pts.– secondary or tertiary patients – be aware that antithrombic therapy withdrawal is potentially dangerous.
2. ALWAYS check inflammation (include Ox-LDL) prior to discontinuation. If ‘hot’ postpone surgery, if possible.
3. Discuss with surgeon – attempt to keep antithrombotic medication in place during surgery if possible – balance risk vs benefit.
4. Be aware of BMS vs DES and implications for antiplatelet therapy.

Metformin for Non-diabetic CAD Pts to Reduce CV Risk??

Metformin: No CV Benefit in Non-diabetics

- Randomized double blind placebo trial; 173 non-DM CAD pts; all on statins; metformin 875mg bid or placebo; 18 mos.

- Primary endpoint: cIMT progression

Preiss, D., et. al. (2013). Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. *The Lancet Diabetes & Endocrinology*. doi: 10.1016/s2213-8587(13)70152-9

Metformin: No CV Benefit in Non-diabetics

- No significant difference in cIMT progression:

  0.007 mm per year- (95% CI,–0.006 to 0.020)

  p=0.29

- No significant change in plaque score:

  0.01 per year- (95% CI, –0.23 to 0.26)

  p=0.92

Preiss, D., et. al. (2013). Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. *The Lancet Diabetes & Endocrinology*. doi: 10.1016/s2213-8587(13)70152-9

Metformin: No CV Benefit in Non-diabetics

- Secondary endpoints improved with met:

  HbA1c, fasting insulin, HOMA-IR, tPA, adiposity, GGT

- Secondary endpoints not improved with met:

  TC, HDL, non-HDL, TG, FBG, hs-CRP, hs-cTnT, Alt

Preiss, D., et. al. (2013). Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. *The Lancet Diabetes & Endocrinology*. doi: 10.1016/s2213-8587(13)70152-9

Metformin: No CV Benefit in Non-diabetics

Current evidence does not support recommending metformin for CV benefit in non-diabetic high CV risk pts on statins.

Preiss, D., et. al. (2013). Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. *The Lancet Diabetes & Endocrinology*. doi: 10.1016/s2213-8587(13)70152-9

BDM Thoughts

- Supports concept that reduction in CV risk requires impact on arterial inflammation.

Medical Management Superior to Stenting for Recurrent Stroke Prevention

- 451 pts post TIA or stroke from major intracranial artery stenosis; randomly assigned to medical rx alone or plus stenting of culprit stenosis; median follow-up 32.4 months

- Primary endpoint: stroke or death within 30 days after enrolment, IS in the territory of the qualifying artery beyond 30 days of enrolment, or stroke or death within 30 days after a revascularization procedure of the qualifying lesion during follow-up.

Derdeyn, C. P., et. al. (2013). Aggressive medical treatment with or without stenting in high-risk patients with intracranial artery stenosis (SAMMPRIS): the final results of a randomised trial. *The Lancet*. doi: 10.1016/s0140-6736(13)62038-3

Medical Management Superior to Stenting for Recurrent Stroke Prevention

Medical rx essential elements:

a) dual antiplatelet therapy- ASA & clopidogrel X 90 days

b) systolic BP rx goal < 140 mmHg & <130 in DM

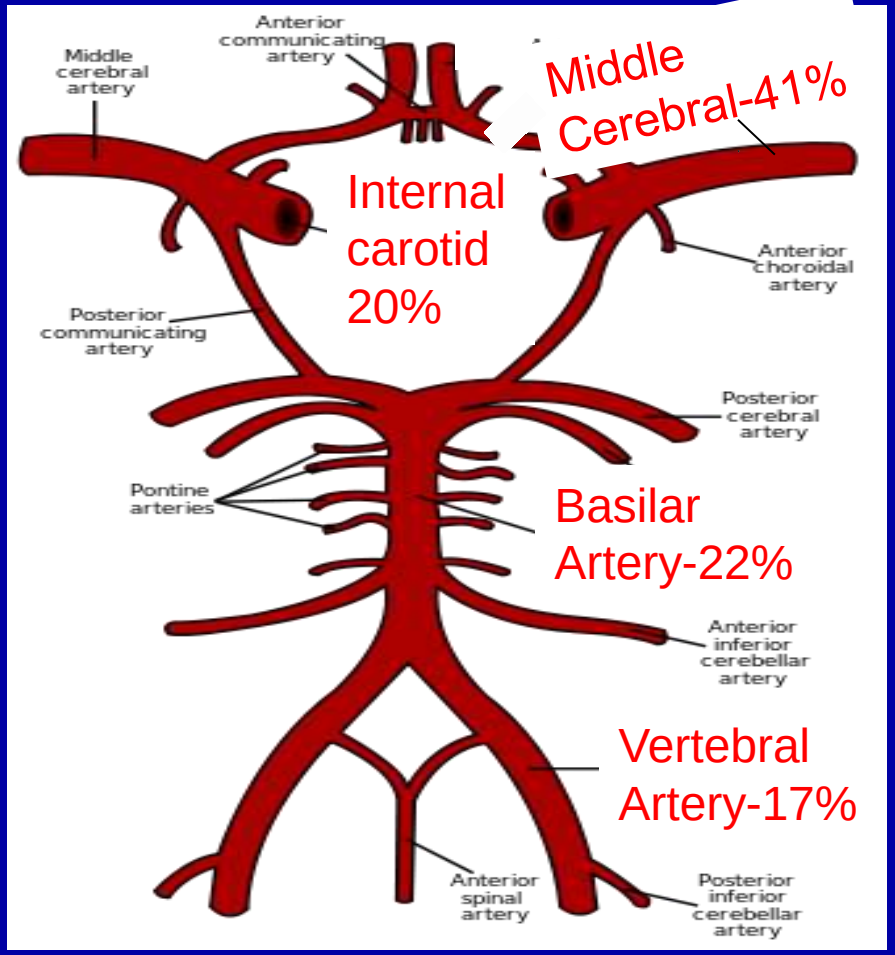
c) LDL-C rx goal < 70mg/dL- rosuvastatin provided

d) lifestyle program for diet, weight, exercise and nicotine

e) secondary targets for DM and non-HDL

Derdeyn, C. P., et. al. (2013). SAMMPRIS. *The Lancet*. doi: 10.1016/s0140-6736(13)62038-3

Medical Management Superior to Stenting for Recurrent Stroke Prevention



Derdeyn, C. P., et. al. (2013). SAMMPRIS. *The Lancet*. doi: 10.1016/s0140-6736(13)62038-3

Medical Management Superior to Stenting for Recurrent Stroke Prevention

34 (15%) of medical rx alone pts and 52 (23%) of medical rx plus stenting pts had a primary endpoint event.

Medical rx alone pts had significantly less risk with a p value of 0.0252

Results driven by any stroke and major hemorrhagic events

Derdeyn, C. P., et. al. (2013). SAMMPRIS. *The Lancet*. doi: 10.1016/s0140-6736(13)62038-3

Medical Management Superior to Stenting for Recurrent Stroke Prevention

Results illustrate medical management can significantly mitigate the high recidivistic risk on post TIA and stroke pts with intracranial (internal carotid, middle cerebral, basilar and vertebral) arterial stenosis.

Derdeyn, C. P., et. al. (2013). SAMMPRIS. *The Lancet*. doi: 10.1016/s0140-6736(13)62038-3

Medical Therapy for Renal Artery Stenosis as Opposed to Stenting

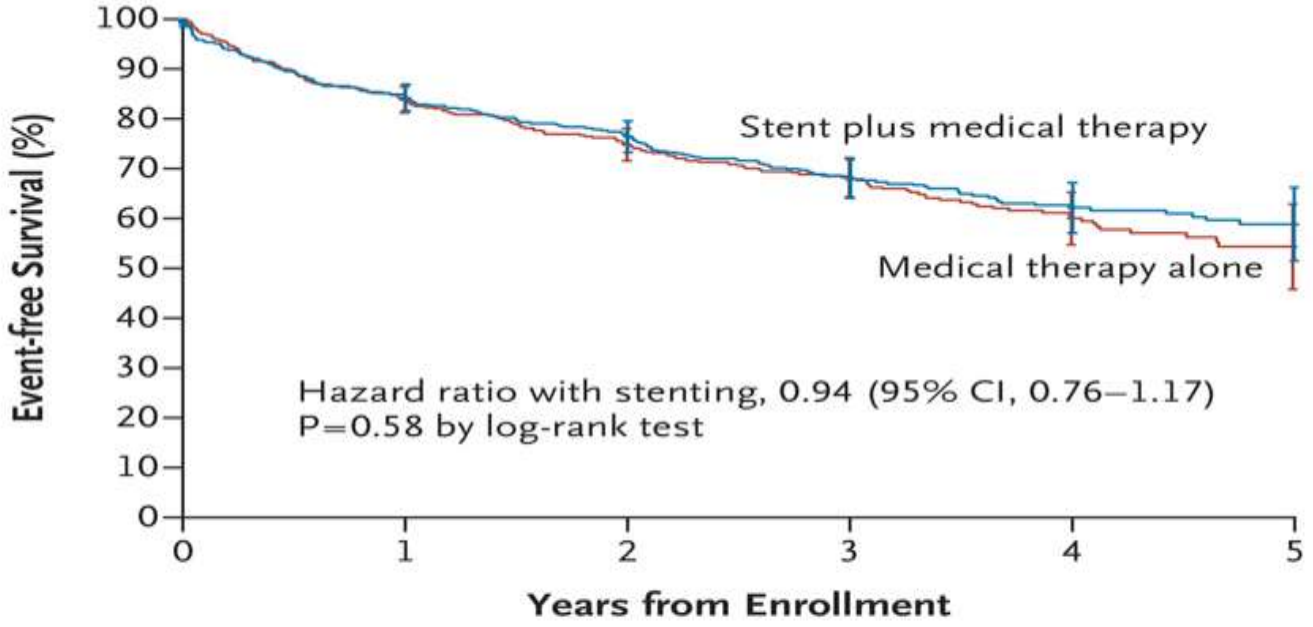
- 947 pts with renal-artery stenosis were assigned to renal-artery stenting or medical therapy follow-up median 43 mos.

- Mandated meds: candesartan with or without Hctz; amlodipine–atorvastatin with the dose adjusted to achieve BP <140/90 or <130/80 in DM or CKD & LDL<100 mg/dL; antiplatelet rx; DM rx as per guidelines.

Cooper, C. J., et. al. (2014). Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. *N Engl J Med*. 370(1):13-22

Medical Therapy for Renal Artery Stenosis as Opposed to Stenting

Kaplan–Meier Curves for the Primary Outcome.



No. at Risk

Medical therapy alone	472	371	314	214	115	40
Stent plus medical therapy	459	362	318	224	131	59

Cooper, C. J., et. al. (2014). Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. *N Engl J Med*. 370;1:13-22

Clinical End Points.

Table 2. Clinical End Points.*

End Point	Stenting plus Medical Therapy (N=459)	Medical Therapy Only (N=472)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary end point: death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or permanent renal-replacement therapy†	161 (35.1)	169 (35.8)	0.94 (0.76–1.17)	0.58
Components of primary end point‡				
Death from cardiovascular or renal causes	20 (4.4)	20 (4.2)		
Stroke	12 (2.6)	16 (3.4)		
Myocardial infarction	30 (6.5)	27 (5.7)		
Hospitalization for congestive heart failure	27 (5.9)	26 (5.5)		
Progressive renal insufficiency	68 (14.8)	77 (16.3)		
Permanent renal-replacement therapy	4 (0.9)	3 (0.6)		
Secondary clinical end points§				
Death from any cause	63 (13.7)	76 (16.1)	0.80 (0.58–1.12)	0.20
Death from cardiovascular causes	41 (8.9)	45 (9.5)	0.89 (0.58–1.36)	0.60
Death from renal causes	2 (0.4)	1 (0.2)	1.89 (0.17–20.85)	0.60
Stroke	16 (3.5)	23 (4.9)	0.68 (0.36–1.28)	0.23
Myocardial infarction	40 (8.7)	37 (7.8)	1.09 (0.70–1.71)	0.70
Hospitalization for congestive heart failure	39 (8.5)	39 (8.3)	1.00 (0.64–1.56)	0.99
Progressive renal insufficiency	77 (16.8)	89 (18.9)	0.86 (0.64–1.17)	0.34
Permanent renal-replacement therapy	16 (3.5)	8 (1.7)	1.98 (0.85–4.62)	0.11

* The hazard ratios were calculated with the use of multivariable proportional-hazards regression. P values were calculated with the use of the log-rank statistic.
† Only the first event per participant is included in the composite.
‡ Components of the composite are included only if it was the first event contributing to the primary end point.
§ The first event for each component of the primary composite end point is included as a secondary end point.

Cooper CJ et al. N Engl J Med 2014;370:13-22

The NEW ENGLAND JOURNAL of MEDICINE

Medical Therapy for Renal Artery Stenosis as Opposed to Stenting

Table 2. Clinical End Points.*

End Point	Stenting plus Medical Therapy (N=459)	Medical Therapy Only (N=472)	Hazard Ratio (95% CI)	P Value
	no. (%)			
Primary end point: death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or permanent renal-replacement therapy†	161 (35.1)	169 (35.8)	0.94 (0.76–1.17)	0.58
Components of primary end point‡				
Death from cardiovascular or renal causes	20 (4.4)	20 (4.2)		
Stroke	12 (2.6)	16 (3.4)		
Myocardial infarction	30 (6.5)	27 (5.7)		
Hospitalization for congestive heart failure	27 (5.9)	26 (5.5)		
Progressive renal insufficiency	68 (14.8)	77 (16.3)		
Permanent renal-replacement therapy	4 (0.9)	3 (0.6)		
Secondary clinical end points§				
Death from any cause	63 (13.7)	76 (16.1)	0.80 (0.58–1.12)	0.20
Death from cardiovascular causes	41 (8.9)	45 (9.5)	0.89 (0.58–1.36)	0.60
Death from renal causes	2 (0.4)	1 (0.2)	1.89 (0.17–20.85)	0.60
Stroke	16 (3.5)	23 (4.9)	0.68 (0.36–1.28)	0.23
Myocardial infarction	40 (8.7)	37 (7.8)	1.09 (0.70–1.71)	0.70
Hospitalization for congestive heart failure	39 (8.5)	39 (8.3)	1.00 (0.64–1.56)	0.99
Progressive renal insufficiency	77 (16.8)	89 (18.9)	0.86 (0.64–1.17)	0.34
Permanent renal-replacement therapy	16 (3.5)	8 (1.7)	1.98 (0.85–4.62)	0.11

* The hazard ratios were calculated with the use of multivariable proportional-hazards regression. P values were calculated with the use of the log-rank statistic.
† Only the first event per participant is included in the composite.
‡ Components of the composite are included only if it was the first event contributing to the primary end point.
§ The first event for each component of the primary composite end point is included as a secondary end point.

Primary endpoints: CV death; renal death; MI; stroke; CHF hospitalization; progressive renal disease; permanent dialysis or renal transplant

Cooper, C. J., et. al. (2014). *N Engl J Med*. 370;1:13-22

Medical Therapy for Renal Artery Stenosis as Opposed to Stenting

Stenting did not provide any significant benefit when added to comprehensive, multifactorial medical therapy.

Medical therapy without stenting is the preferred management strategy for renal-artery stenosis.

Cooper, C. J., et. al. (2014). Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis. *N Engl J Med*. 370;1:13-22

BDM Thoughts

- These studies demonstrate the power of medical management (OMT) to prevent CV events.

- Compatible with results of studies like COURAGE which demonstrate OMT is as good as a stent in stable CAD.

Cases: We have one!!

- 71 yo DM wm; Type II DM for 10+ yrs; BP; hyperlipidemia; obesity (BMI 32).

- CV hx: CAD -CABG ’86; ? Vertebrobasilar TIA mid-2012; CVD- endarterectomy left carotid ‘12; PAD- aortofemoral -popliteal bypass ’13

- 9/13; severe burns/heating pad to legs; grafting

- Meds: aspirin 81 mg – yrs
  simvastatin 40 mg qd - yrs
  lisinopril 20 mg qd – yrs
  amolodipine 10 mg – yrs
  Novolog 30 units sc tid
  metformin 500 mg bid
  levothyroxine 100 mcg qd
  fish oil started mid-2013
  carvedilol – started 11/2013
  pioglitazone – started 11/2013

Last labs 7/2013

HbA1c 6.9%

TC- 164

TG- 166

HDL- 39

LDL- 91

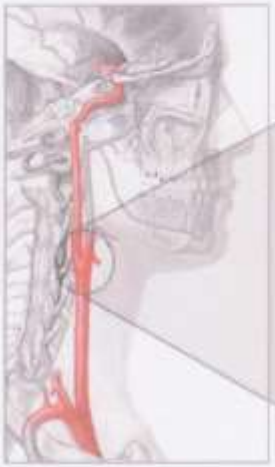
TC/HDL= 4.2

TG/HDL= 4.3

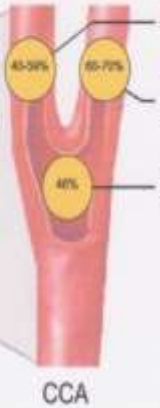
Systolic BP/ABI – 146 right and 148 left

Visualized Plaque and Atherosclerotic Burden Assessment

Name: **DOB:** 3/12/42 **Age:** 70 **Gender:** Male **Date:** 6/22/12

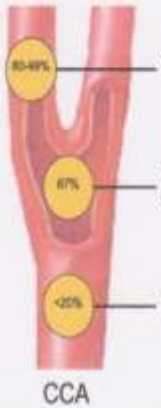


Right — Plaque Description



- 4.979mm Heterogeneous
- 1.721mm Heterogeneous
- 2.404mm Heterogeneous
- 3.384mm Heterogeneous
- 3.713mm Heterogeneous

Left — Plaque Description



- 2.028mm Heterogeneous
- 2.709mm Heterogeneous
- 3.575mm Heterogeneous
- 1.885mm Heterogeneous

*Plaque noted above was measured through arterial area diameter reduction, which is deliberated by measuring the circumference of the outside of the vessel subtracting any visible stenosis.

*Carotid velocities provided on reverse.

Carotid - IMT

Your average Carotid-IMT is **0.852**

You are a *70* year old with arteries of a **70** year old Male.

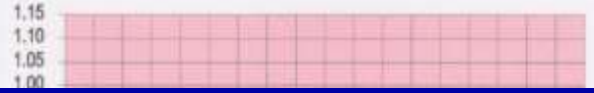
This graph indicates your percentile score for similar sex and age.

A C-IMT of less than 0.60mm is generally considered healthy.

Current CIMT Measurement

Date	Age	CIMT	Percentile
Jun 2012	70	0.852	50th

Mean Distal 1 cm CCA IMT of General Population with No Coronary Heart History



Carotid Duplex 1 Month Later

Right carotid with moderate plaque in ICA and bifurcation with a 16 to 49% stenosis ICA.

Left carotid with moderate plaque in ICA abd bifurcation with 50 to 79% stenosis ICA.

EDFROG

Education: make sure pt understands ‘event reality’

Disease: CAD, CVD, PAD – secondary; no actual sx’ic events; ?? silent ones??

Fire: unknown

Roots: IR; hyperlipidemia; ????? PD; endodontic disease; sleep issues; vit. D; psychosocial; lipo (a); genetic

Optimal: lots missing data including hs-cTnI

Genetics: ????; if + 9p21 – tight glycemic control; haptaglobin for ? vit. E; CYP2c19 for clopidogrel; apoE for diet

IRA

Management: cornerstones –

1) Lifestyle –???????- exercise; diet; nicotine; soda; stress; sleep; oral hygiene

2) antiplatelet; PAD- should be on clopidogrel; is he responding???

AHA statement post CHARISMA

Patients who are candidates for clopidogrel

- Post MI
- Post angioplasty for MI or unstable angina
- Post stent
- Post TIA or ischemic stroke
- PAD

Updated AHA Statement. 3/16/2006. www.americanheart.org

IRA

Management: cornerstones –

1) Lifestyle –???????- exercise; diet; nicotine; soda; stress; sleep; oral hygiene

2) antiplatelet; PAD- should be on clopidogrel; is he responding???

3) Statin – simvastatin 40mg – something should change

Simvastatin Restrictions

- Do not exceed 20 mg simvastatin daily with:
  - Amlodipine
  - Ranolazine

FDA Safety Announcement 6/8/2011

IRA

Management: cornerstones –

1) Lifestyle –???????- exercise; diet; nicotine; soda; stress; sleep; oral hygiene

2) antiplatelet; PAD- should be on clopidogrel; is he responding???

3) Statin – simvastatin 40mg

4) RAAS –on two other BP meds (amlodipine and carvedilol) with no diuretic on board; Lisinopril - ? change to ramipril

Ramipril Improves PAD

- 212 PAD pts.; mean age 65.5; RDBPC trial 10 mg/d of ramipril (n=106) or matching placebo (n=106) for 6 months
- Ramipril increased pain-free walking 77% and maximum walking time 123%
- The only 2 drugs FDA approved for PAD - pentoxifylline and cilostazol – increase walking distance by 15%-25% respectively.

Ahimastos, A., Walker, P., et al. JAMA, 2.6.2013. Vol 309, Nol. 5 453-460

IRA

Reassess biomarkers:

Lipids including lipo (a); inflammatory markers; NT-pro-BNP; hs-cTnI; vit. D; CMP- creatinine, K+, TB, hepatic enzymes; thyroid; aspirin response

Evaluate for: PD; endodontic disease; sleep issues; vit. D; psychosocial; lipo (a); genetic

IRA

Anchor in annual disease monitoring (CIMT):

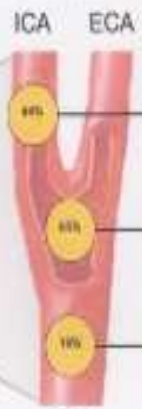
Do not really know much other than last labs showed decent glycemic control and sub-optimal basic lipids. The blood pressure is also high.

Any guesses as to how that is doing??????????????

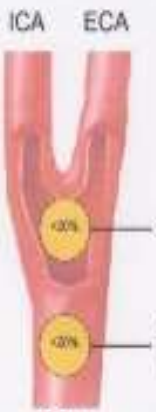
Visualized Plaque and Atherosclerotic Burden Assessment

Name _____ DOB: 3/12/42 Age: 71 Gender: Male Date: 12/19/13

Right — Plaque Description



Left — Plaque Description



*Plaque noted above was measured through arterial area diameter reduction, which is deliberated by measuring the circumference of the outside of the vessel subtracting any visible stenosis.

*Carotid velocities provided on reverse.

Carotid - IMT

Your average Carotid-IMT is **1.465**

You are a 71 year old with arteries of a **65** year old Male.

This graph indicates your percentile score for similar sex and age.

A C-IMT of less than 0.60mm is generally considered healthy.

Current and Previous CIMT Measurements

Date	Age	CIMT	Percentile
Dec 2013	71	1.465	>95th
Jun 2012	70	0.852	50th

Mean Distal 1 cm CCA IMT of General Population with No Coronary Heart History

1.16

CIMT	6/2012	12/2013
Mean CCA IMT	0.852 mm	1.465 mm
R-ICA	5.0 mm H	5.6 mm H
R- bifurc	3.4 mm H	3.0 mm H
R- CC	-----	3.2 mm H
L-ICA	2.0 mm H	---------
L-bifurc	2.7 mm H	2.1 mm H
L-CC	1.9 mm H	2.0 mm H

Carotid duplex	7/2012	7/2013
R – ICA & bifurcation	Moderate plaque	Moderate plaque
R – ICA stenosis	16-49%	16-49%
L – ICA & bifurcation	Moderate plaque	No plaque
L- ICA stenosis	50-79%	None

Comparing the two, I would question the huge advance in CCA IMT

Conclusions:

- Numerous missing pieces of information and definite fine tuning needed.
- A comprehensive EDFROG-IRA approach, should enhance this patient's future.

Upcoming Presentations

Upcoming Presentations

- 2/13/2014 – morning TV talk show on WBRZ-ABC; Amy and Brad
- 2/15/2014- Barnes and Noble book signing Lubbock, TX; Amy and Brad
- 2/20/2014 – Auntie's Book Store signing Spokane, WA; Amy and Brad
- 2/22/2014 – Women's luncheon with some book stars; Amy – Brad in corner ☺
- 3/1/2014 – Barnes and Noble book signing Elizabethtown, KY- Brad
- 3/21-22/2014 – BDM Preceptorship & book signings LV, NV

Open for Discussion