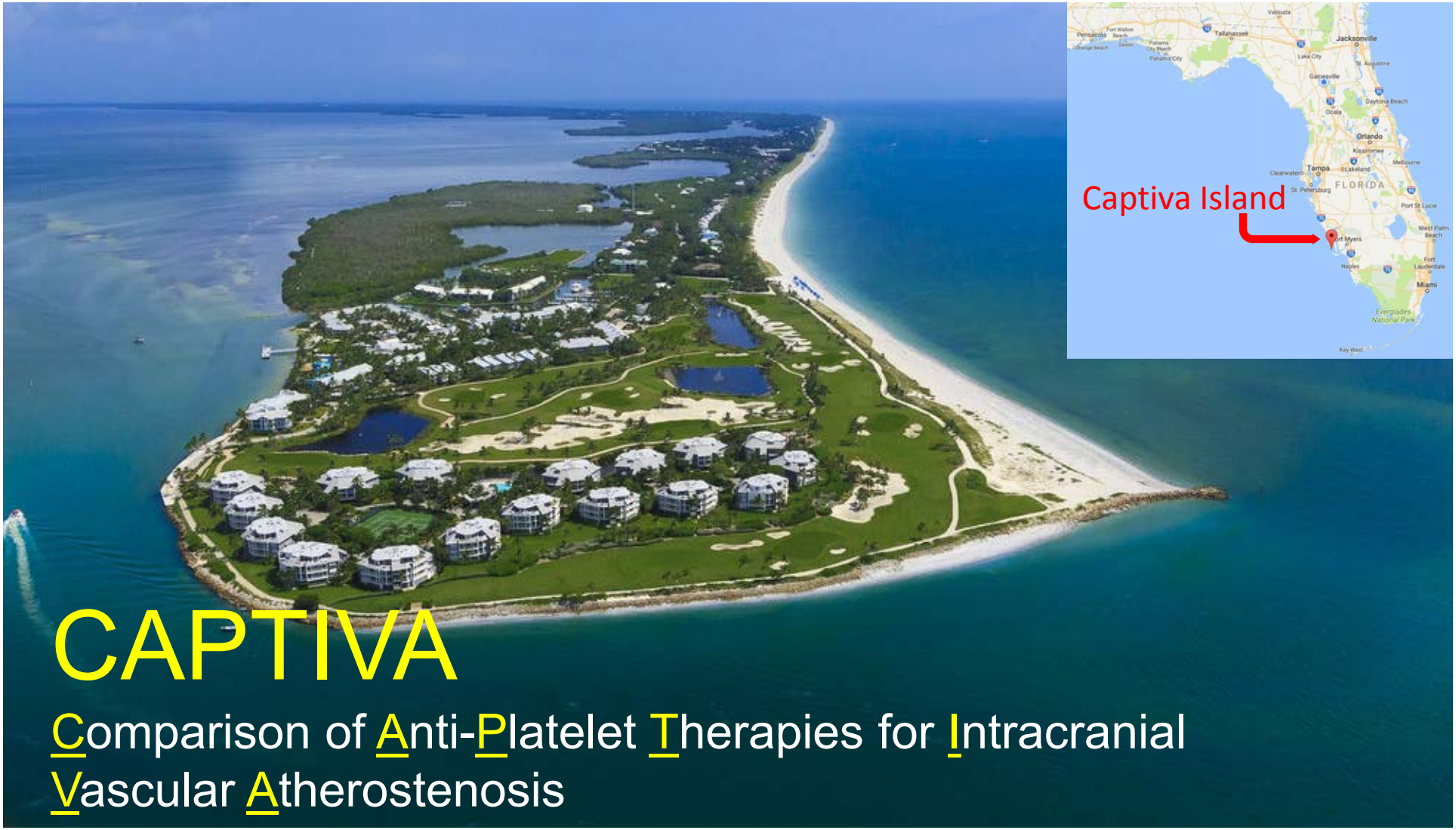

CAPTIVA

Comparison of Anti-Platelet Therapies for Intracranial Vascular Atherostenosis

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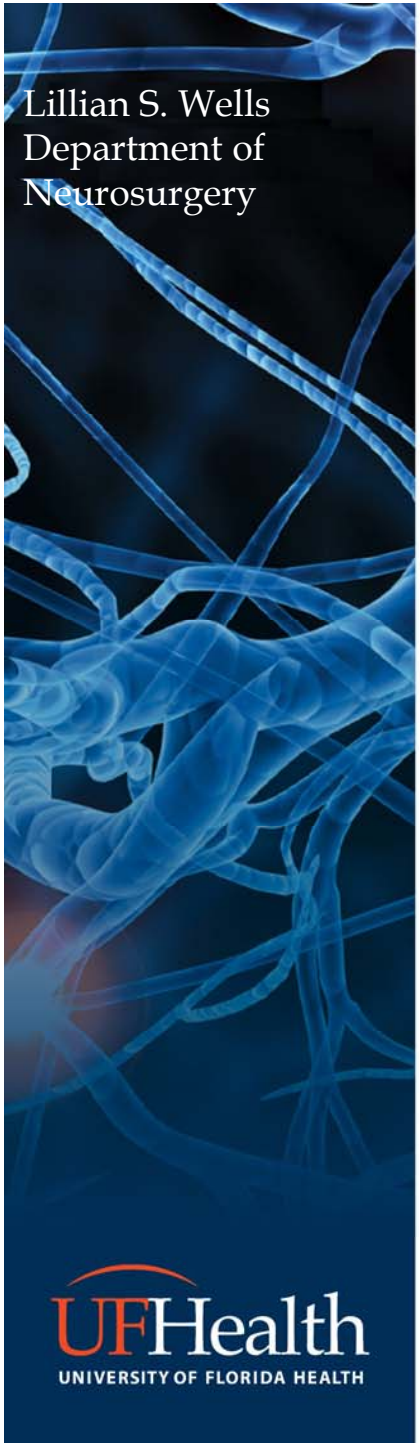
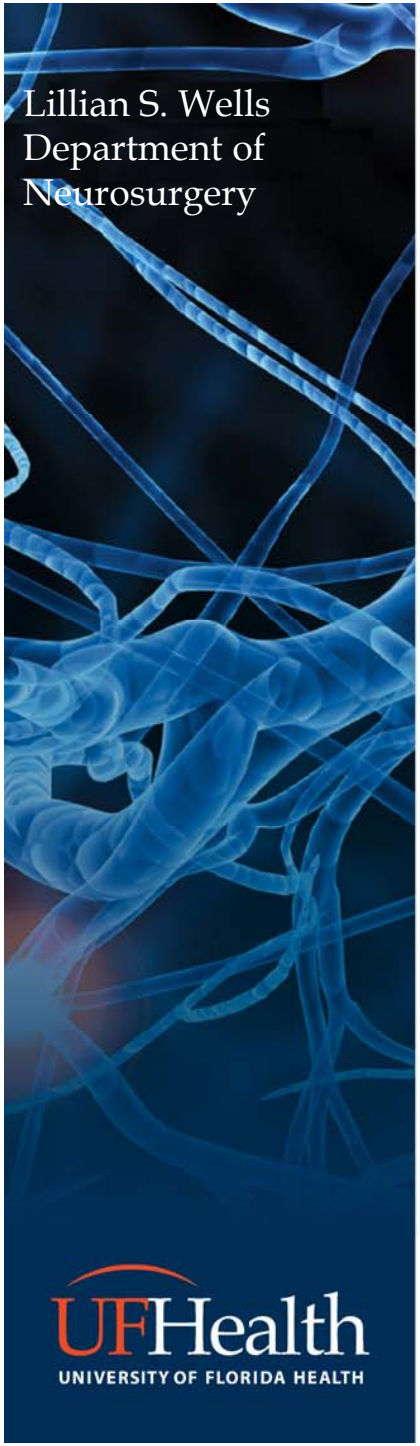


ICAD

- sICAD: one of most common causes of stroke worldwide[1]
- 8-10% of strokes in the US[2] (~80,000 per year)
- SAMMPRIS: randomized 451 sICAD patients to stenting vs medical management[3]
  - 27% one-year symptomatic infarct or death in medical arm subjects who qualified by symptomatic infarct[4]
- *Clearly there is a need for better treatment*

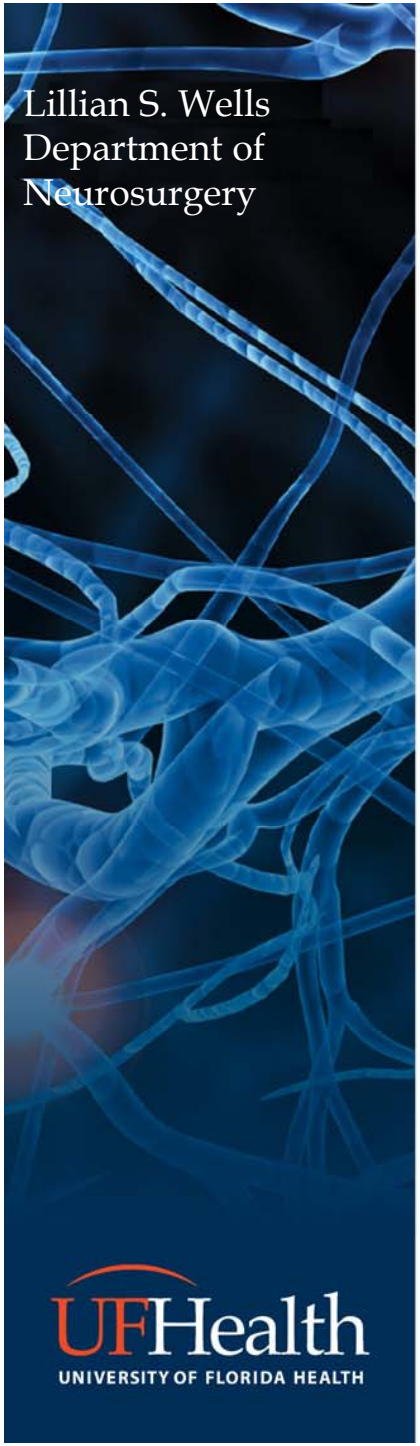
1. Gorelick et al, Stroke 2008
2. Sacco et al, Stroke 1997
3. Chimowitz et al, NEJM 2011
4. Lynn & Chimowitz, personal communication



Dual Anti-Platelet (DAPT)

- CHANCE randomized 5170 minor stroke/TIA patients to aspirin+clopidogrel vs aspirin alone[1]
- Strongly suggested DAPT most beneficial in sICAD and virtually made no difference in small vessel disease[2]
- Study of 200 Chinese subjects with sICAD and ECAD randomized to DAPT vs aspirin: stroke 9.1% vs 27.9%[3] (50mg: 95%CI 1.704-23.779, P<0.05)(75mg: 95%CI 1.190-13.240, P<0.05)

1. Wang et al, NEJM 2013
2. Liu et al, Neurology 2015
3. Zuo et al, Medicine 2017



Ticagrelor

- P2Y12 inhibitor, new class of drug cyclopentyl-triazolo-pyrimidine (clopidogrel, prasugrel, ticlopidine are thienopyridines)
- Not a pro-drug, does not require hepatic CYP2C19 activation
- Faster onset of action, greater suppression of platelet activity than clopidogrel[1,2]
- Pleiotropic off-target effects: increase in plasma adenosine which has vasodilatory properties and exerts further platelet inhibition[3,4]

1. Storey et al, JACC 2010
2. Gurbel et al, Circulation 2009
3. Bonello et al, JACC 2014
4. Nylander et al, J Thromb Haemostasis 2013

Ticagrelor: ACS and ICAD

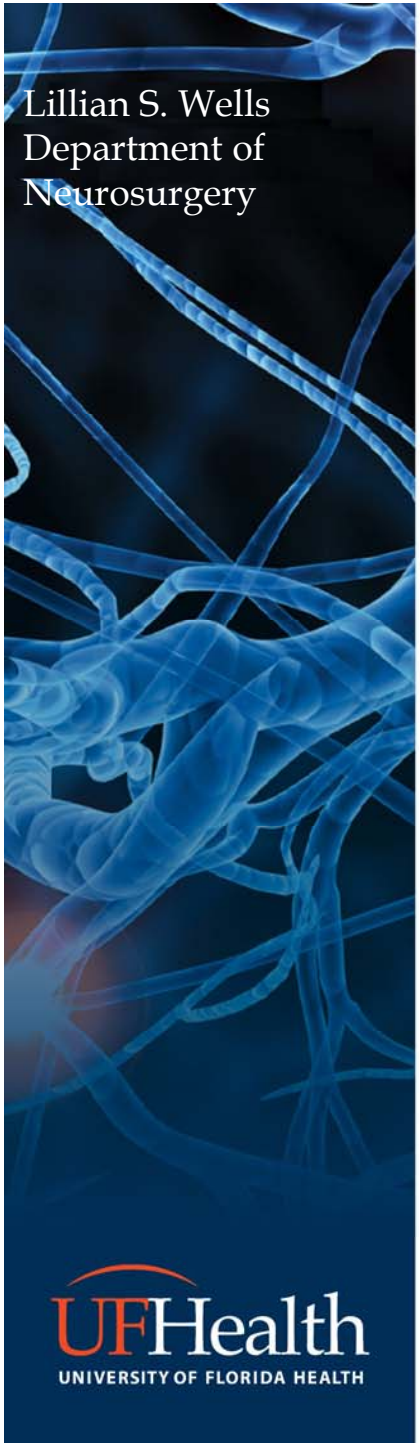
- PLATO: randomized 18,624 ACS patients to ticagrelor vs clopidogrel: ticagrelor reduced one-year vascular death, MI, or stroke (9.8% vs 11.7%, P<0.001)[1]
- PRINCE: randomizing Chinese patients with high-risk TIA or minor stroke to ASA+ticagrelor vs ASA+clopidogrel: 90-day stroke 4.6% (ticagrelor) vs 7.5% (clopidogrel)[2]
- (High prevalence of ICAD in Asian populations)

1. Wallentin et al, NEJM 2009
2. Wang et al, presented at ISC Feb 2017

Ticagrelor: Stroke Prevention

- SOCRATES: randomized 13,199 patients with TIA or minor stroke to ticagrelor vs aspirin
  - Failed to show superiority in preventing primary endpoint (composite of stroke, MI, death) 6.7% vs 7.5%[1]
  - Ischemic stroke: ticagrelor 5.8% vs aspirin 6.7% (HR 0.87; 95% CI 0.76 to 1.00; nominal P=0.046)[1]
  - Asian subjects primary endpoint: ticagrelor 9.6% vs aspirin 11.6% (HR 0.81; 95% CI 0.67–0.99, nominal P=0.04)[2]
  - Subjects with TIA/stroke due to atherosclerotic disease: ticagrelor 6.7% vs aspirin 9.6% (HR 0.68, 95% CI 0.53-0.88, P=0.003)[3]

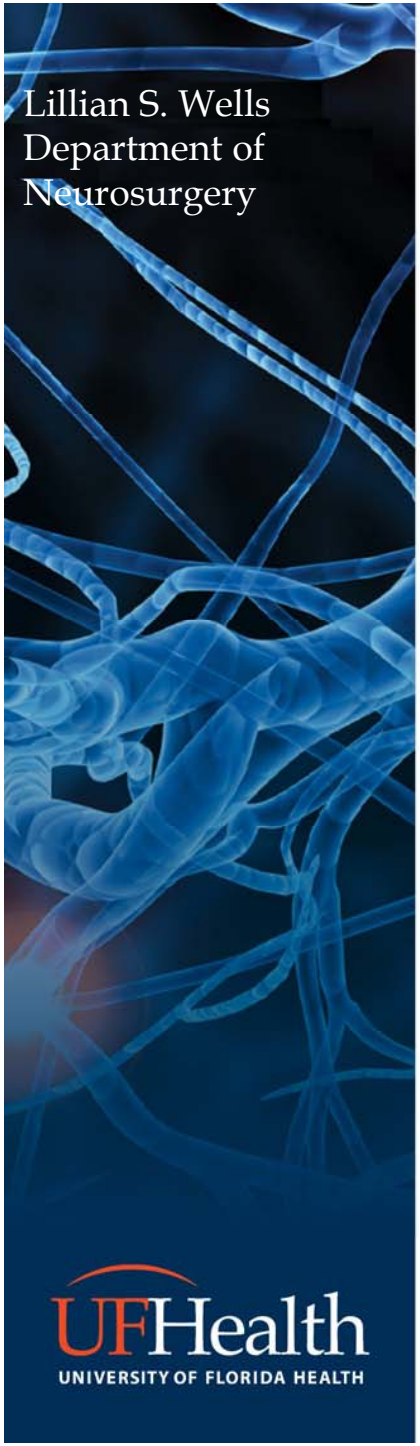
1. Johnston et al, NEJM 2016
2. Wang et al, Stroke 2017
3. Amarenco et al, Lancet Neurology 2017



CYP2C19

- Clopidogrel: pro-drug, requires cytochrome P450 2C19 (CYP2C19) enzymatic activation
- 30% population carriers *CYP2C19* single nucleotide LOF polymorphism (*2, *3) (*8 is also LOF) and thus have reduced clopidogrel efficacy
- Multiple meta-analyses of ACS/PCI patients: LOF carriers significantly increased risk of cardiovascular death, MI, stroke, or stent thrombosis[1-6]

1. Dahabreh et al, AHRQ 2013
2. Sofi et al, Pharmacogen 2011
3. Mega et al, JAMA 2010
4. Jang et al, Am J Card 2012
5. Zhang et al, Thromb Res 2015
6. Mao et al, Arch Card Dis 2013



CYP2C19: Stroke

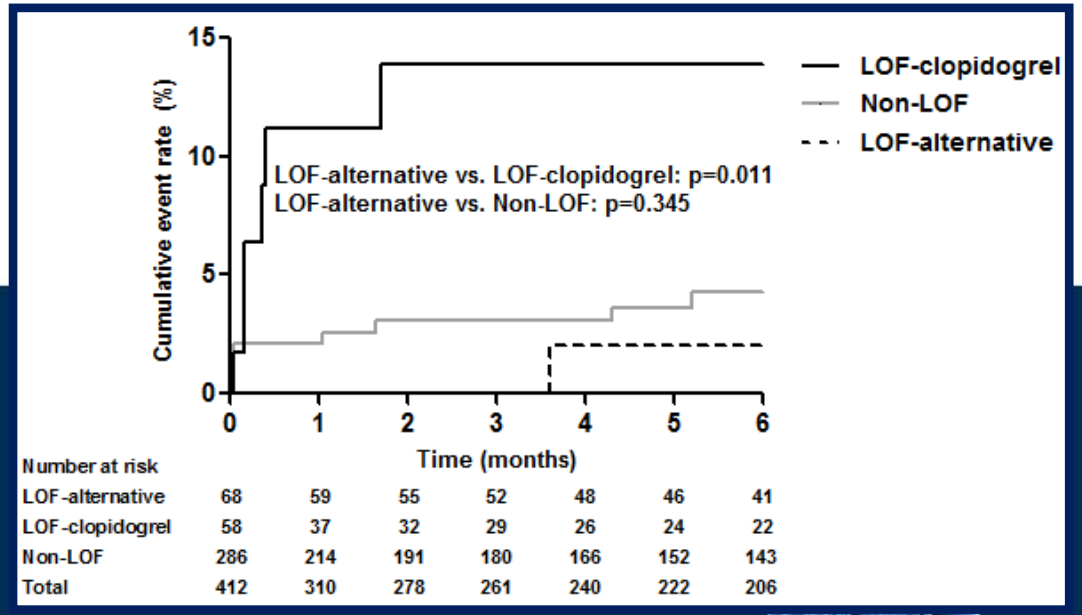
- CHANCE: 2933 patients with *CYP2C19* genotyping[1]

	LOF Non-Carriers	**LOF Carriers**
90-day recurrent stroke	**6.7% aspirin+clopidogrel** **12.4% aspirin** **P=0.02**	9.4% aspirin+clopidogrel 10.8% aspirin P=NS
Secondary composite endpoint (ischemic stroke, hemorrhagic stroke, vascular death)	**6.7% aspirin+clopidogrel** **12.5% aspirin** **P=0.02**	9.4% aspirin+clopidogrel 10.9% aspirin P=NS
90-day recurrent stroke in subjects w/large artery atherosclerosis	**5.3% aspirin+clopidogrel** **7.9% aspirin** **P=0.04**	6.6% aspirin+clopidogrel 6.3% aspirin P=NS

1. Wang et al, JAMA 2016

CYP2C19-Guided Therapy (UF)

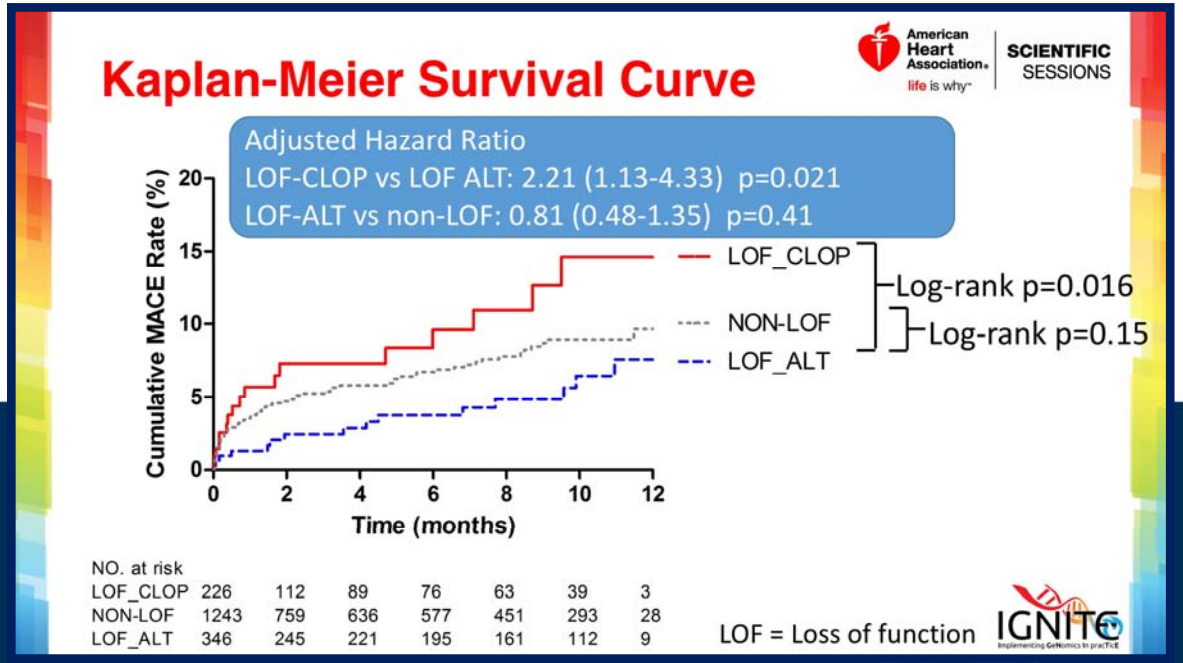
- Prospective study of 412 PCI patients at UF[1]
- LOF carriers treated with CYP2C19-guided antiplatelet therapy (switch to prasugrel, ticagrelor, or triple-dose clopidogrel)
  - Risk of major adverse cardiovascular events (MACE) similar to non-carriers treated with clopidogrel
  - 86% relative risk reduction compared to LOF carriers treated with standard clopidogrel: risk of MACE: LOF-alternative (2%), non-LOF-clopidogrel (4%), LOF-clopidogrel (14%) (HR 0.09, 95% CI 0.01-0.84, p=0.035)



1. Cavallari et al, Circulation 2015

CYP2C19-Guided Therapy (Multicenter)

- Prospective study of 1815 PCI patients at 7 sites[1]
- LOF carriers treated with CYP2C19-guided alternative antiplatelet therapy (LOF-alt)
- MACE risk was significantly higher in LOF-clop patients compared with LOF-alt patients (HR: 2.3, 95% CI: 1.2-4.5; p=0.0154).



1. Cavallari et al, Circulation 2016

CAPTIVA: Aims

- Primary Aim: To determine the efficacy of aspirin+ticagrelor compared to aspirin+clopidogrel in preventing one-year symptomatic cerebral infarct or death in patients with symptomatic 70-99% intracranial stenosis
- Secondary Aim: To explore whether the treatment effect varies according to *CYP2C19* loss-of-function allele carrier status.

CAPTIVA Design

- Phase 3 prospective multicenter double-blinded randomized controlled trial
- NIH StrokeNET
- 4-year subject recruitment period with 12 month followup

CAPTIVA Design: Subjects

- Subjects: Age≥30, non-severe symptomatic infarct within 30 days of enrollment attributable to 70-99% stenosis of major intracranial artery (ICA, M1, vertebral artery, basilar artery)
  - Non-severe: mRS≤3
  - Without significant aphasia
  - Symptomatic infarct: AHA/ASA definition, includes CITS
  - % stenosis by CTA or MRA

CAPTIVA Design: Treatment Arms

- All subjects will receive intensive medical management (INTERVENT, SBP<140, LDL<70, antihypertensive, atorvastatin)
- Subjects will be randomized to:
  - Aspirin 325mg QD + ticagrelor (180mg loading dose on day 1, 90mg BID thereafter) for 90 days, after which aspirin alone to close-out at 1 year
  - Or aspirin 325mg QD + clopidogrel 75mg QD for 90 days, after which aspirin alone to close-out at 1 year

CAPTIVA Design: Randomization & Blinding

- Covariate adaptive randomization scheme to ensure treatment balance among carriers and non-carriers
- Double-blinded with double “dummy” placebo pills

CAPTIVA Design: Genotyping

- Enrolled subjects will have blood (or saliva) sample sent to UF Center for Pharmacogenomics
- Samples genotyped for CYP2C19 *2, *3, *8, *17 (also have capability to test for *4, *5, *6)
- Total turnaround time <72 hours (in meantime, patients treated with aspirin+clopidogrel)
- Treating physicians, patients, and investigators will be blinded to genotype
- Subjects will be randomized after central reader enters genotype

CAPTIVA Design: Endpoints

- Primary: any symptomatic infarct (AHA/ASA definition, includes CITS) or death within 12 months
- Secondary: any severe bleeding within 12 months

CAPTIVA Sample Size

- Two-sample survival analysis comparing time-to-event of two randomized treatment arms
- Medical arm of SAMMPRIS: 27% one-year symptomatic infarct or death in subjects who qualified by stroke[1]
- CTA or MRA may overestimate stenosis, so assume lower event rate 24% (11% relative risk reduction to SAMMPRIS)
- Survey of US neurologists: would need to see 30% relative risk reduction to switch antithrombotics for sICAD[2]
- PRINCE: 39% relative risk reduction of aspirin+ticagrelor vs aspirin+clopidogrel in preventing stroke[3], thus our hypothesized 30% effect size seems achievable
- To detect 30% risk reduction with 80% power, using a two-sided 0.05 level of significance, and assuming 5% drop-out, and after inflation for two interim analysis for both efficacy and futility, conducted at 50% of the enrolled sample according to an O'Brien-Fleming error spending function, the final sample size is
- 1086 subjects

1. Lynn & Chimowitz, personal communication
2. Turan et al, Cerebrov Dis 2014
3. Wang et al, presented at ISC Feb 2017

CAPTIVA Sample Size for Secondary Aim

- 30% of population are LOF carriers[1]
- CHANCE: 1.4 relative risk of 90-day stroke in LOF carriers vs non-carriers (9.4% vs 6.7%)[2]
- Assume overall 12-month rate of symptomatic infarct or death 24%
  - Then LOF carriers would have 30% event rate
  - Non-carriers would have a 21% event rate
- Assuming a 30% event rate in LOF carriers, a subgroup analysis of LOF carriers (estimated n= .30 X 1086 = 326 subjects) will have 71% power to detect a 40% relative risk reduction, 81% power to detect a 45% relative risk reduction, and 89% power to detect a 50% relative risk reduction
- PRINCE (39% relative risk reduction in stroke regardless of LOF carrier status) suggests our trial will have reasonable power to address the secondary hypothesis as well

1. Mega et al, NEJM 2009
2. Wang et al, JAMA 2016

CAPTIVA Statistical Methods

- All subjects followed for 12 months for primary outcome of any symptomatic infarct or death and analyzed according to intention-to-treat
- Time elapsed between randomization and event occurrence will be calculated
- Subjects who do not experience the event within the 12-month follow-up period will be censored at 12 months
- Subjects who are lost-to-follow-up or withdraw consent will be censored at the time of last patient contact
- The treatment arms will be compared via Cox proportional hazards model, adjusting for carrier status

CAPTIVA Statistical Methods

- Secondary analysis will evaluate treatment effect within subgroups defined by carrier status
- Cox proportional hazards model will be extended to include an interaction between treatment and carrier status
- Based on this model, the treatment effect within each subgroup will be estimated and the corresponding 95% confidence intervals will be constructed

CAPTIVA

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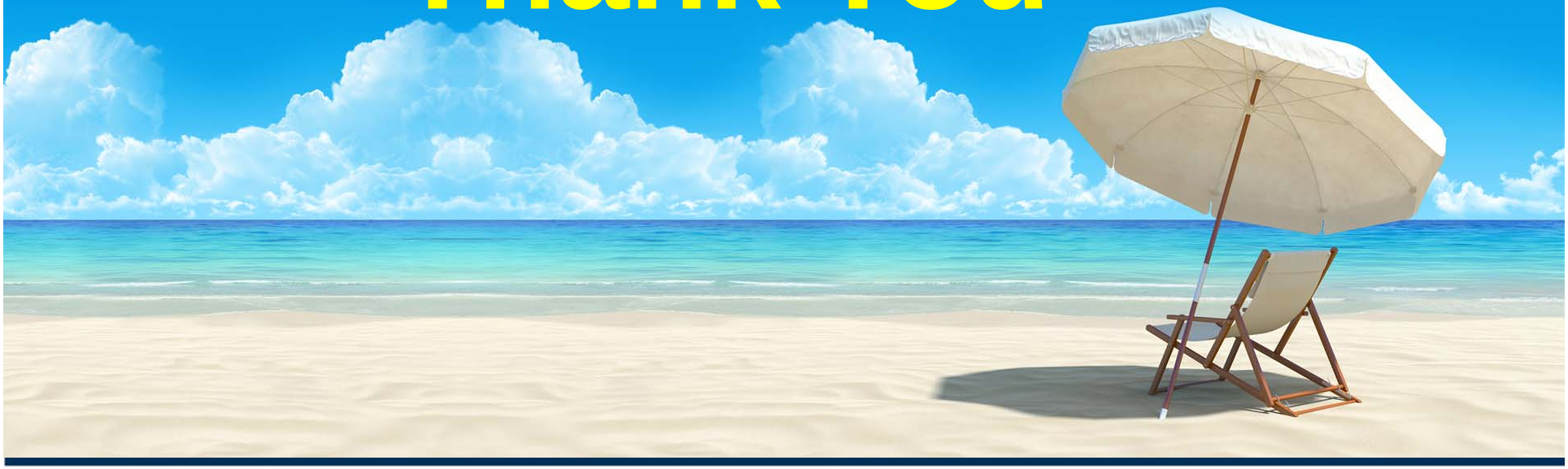
Thank You



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