An Overview of CHARISMA[1,2]

Charisma Trial

- a prospective, multi-center, randomized, double-blind, placebo controlled study of **clopidogrel + ASA** vs **ASA alone** in patients at high risk of atherothrombotic events (with established **cardiovascular disease** or multiple risk factors).
- two treatment arms: ♦ clopidogrel (75mg) + low-dose ASA (75-162mg) daily (n=7802) vs ♦ placebo + low-dose ASA (75-162mg) daily (n=7801); **28months** follow up
- 15,603 patients with baseline characteristics of: ASA 99%, ACE 64%, ARB 26%, statins 77%, beta-blockers 55%, antidiabetic meds 42%, Age 64yrs, male 70%, ↑weight 76% ,prior MI 35%,~2yrs prior , prior stroke 25%,~3months prior, PAD 23%, prior PCI 23%, CABG 20%, carotid endartectomy 5.3%, peripheral vascular surgery or angioplasty 11%.
  - established cardiovascular dx ~78% each arm: documented coronary, cerebrovascular & symptomatic peripheral arterial dx
  - multiple risk factors ~21% each arm (2 major or 3 minor or 1 major & 2minor): Major: Type 1 or 2 **diabetes** 42%; with drug therapy, diabetic nephropathy, ankle-brachial index <0.9, asymptomatic carotid stenosis ≥70% of luminal diameter, ≥1 carotid plaque. Minor: SBP ≥150 mmHg despite therapy for 3months, 1^0 hypercholesterolemia, current smoking >15 cigs/d, male age ≥65 yr & female ≥70 yr

Table 1: CHARISMA results:

Efficacy Endpoints	**Clopidogrel &** Aspirin arm % (n=7802)	Aspirin & **Placebo** arm % (n=7801)	**ARR** %	**RRR** %	**NNT/NNH**	**p value**
1^0 efficacy end point ♥	6.8	7.3	↓0.54	↓7.4	-	0.22
Death from any cause	4.8	4.8	0	0	-	0.90
Stroke (non-fatal)	1.9	2.4	↓0.4	↓20	250	0.05
2^0 efficacy end point ♆	16.7	17.9	↓1.08	↓6	93	0.04
Hospitalization for unstable angina, TIA, or revascularization	11.1	12.3	↓1.2	↓9.8	83	0.02
Safety end points						
Severe bleeding	1.7	1.3	↑0.4	↑0.3	-	0.09
Moderate bleeding	2.1	1.3	↑0.8	↑0.61	125	<0.001

♥**first occurrence of MI, stroke** (of any cause)**,or death from cardiovascular causes** (incl. hemorrhage) **CV**=cardiovascular **Dx**=disease **TIA**=transient ischemic attack
♆ **1^0 endpoints or hospitalization for unstable angina, a TIA, or a revascularization procedure(coronary, cerebral, or peripheral) considered separately.**

Of Note for the Charisma:

- About 10% in both arms of the trial were on open-label clopidogrel. More dropouts, unrelated to adverse events, occurred in the combo vs ASA only arm 20.4 vs 18.2% NNH=46. Overall, **no** significant benefit found (in MI, stroke, or death from CV causes 6.8 vs 7.3%, or even in the individual components) & an ↑ in moderate bleeding (2.1 vs 1.3% **NNH=125** over 28 months) in patients taking the clopidogrel+ASA versus ASA alone. **Subgroup** analysis: suggests some benefit to symptomatic **established** (secondary prevention) CV disease group ↓MI, stroke, or CV death 6.9 vs 7.9% NNT=100, but patients were not clearly differentiated (i.e. both groups had history of CV disease & events). But the multiple **risk factors** (primary prevention) subgroup suggests an ↑ in MI, stroke, or CV death 6.6 vs 5.5% & ↑death 5.4 vs 3.8% NNH=63.

What we knew and what these results add to that knowledge:

- **CAPRIE**[3] found that long-term (mean 2yrs) administration of clopidogrel 75mg od in patients with atherosclerotic vascular disease (defined as recent MI, recent ischemic stroke, or symptomatic peripheral arterial disease-PAD) was slightly more effective (NNT=200) than ASA 325mg od in reducing the risk of ischemic stroke, MI or vascular death. Overall, clopidogrel was more effective in PAD & in diabetics but had less severe GI bleeds 0.5 vs 0.7%, more rashes & ↑expense $93 vs $5/month than ASA alone.
- **CURE**[4] studied the use of clopidogrel (300mg x1 then 75mg od) with ASA (75mg-325mg od) vs ASA, in patients with acute coronary syndromes without ST segment elevation (duration 3-12 months). Results indicate that the combination of clopidogrel and ASA reduced the rates of MI, stroke and death from CV causes more than ASA alone (NNT=48). However, the risk of major bleeding is also increased in patients receiving both medications. (NNH=100 over 9 months). Using **≤100mg/d ASA** ↓bleeding rates.
- **MATCH**[5] compared clopidogrel 75mg od + ASA 75mg od vs clopidogrel 75mg od alone in high risk patients after a transient ischemic attack or ischemic **stroke**. There was no significant benefit ischemic events 15.7 vs 16.7% but a significant increased risk of life-threatening or **major bleeding** (2.6 vs 1.3%)(NNH=77 over 18 months).
- **Plavix & ASA** 81mg od: **useful** in ACS 3-12months (Cure: most benefit in first 3 months of therapy)[6], post stenting 1-12month, PCI[7,8] & acute MI[9,10,11]
- **Plavix & ASA** ~81mg od: **not recommending** use post **stroke** esp. beyond 3 months (Match) & in both established or high **cardiac** risk patients (Charisma); due to **lack of significant efficacy** & ↑ major bleeding. Assessment of the patients **bleeding risk** is critical.

References:

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