

CARDIAC SYMPOSIUM OCTOBER 22 2020



TOP NEW STUDIES IN 2019-2020

ISCHEMIA TRIAL

NLHBI

5179 STABLE ANGINA PATIENTS
MODERATE TO SEVERE ISCHEMIA
3.2 YEARS FOLLOWUP
RANDOMIZED TO INITIAL INVASIVE
OR CONSERVATIVE THERAPY 1:1

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KEY EXCLUSIONS

- 1. RECENT ACS
 - 2. GFR < 30
 - 3. EF < 35%
 - 4. AHA CLASS III OR IV CHF
 - 5. LEFT MAIN STENOSIS (UNPROTECTED) > 50%
- ALL PATIENTS UNDERWENT CTA BY PROTOCOL

INVASIVE TREATMENT GROUP

- GUIDELINE DIRECTED MEDICAL THERAPY
- CATHETERIZATION WITHIN 30 DAYS OF RANDOMIZATION
- REVASCULARIZATION OF ALL ISCHEMIC TERRITORIES IF FEASIBLE
- FFR USE RECOMMENDED
- CABG OR PCI DECISION BY LOCAL HEART TEAM

CONSERVATIVE GROUP

- GUIDELINE DIRECTED MEDICAL THERAPY
- SPECIFIC INTENSIVE PREVENTION WITH TREAT TO TARGET ALGORITHMS
- CTA PERFORMED IN MOST
- IF BECAME UNSTABLE OR REFRACTORY TO MEDICAL TREATMENT COULD UNDERGO CATH

8518 PATIENTS ENROLLED

- BY CTA 1218 DID NOT HAVE OBSTRUCTIVE DISEASE AND DID NOT UNDERGO RANDOMIZATION
- 434 HAD $> 50\%$ LEFT MAIN STENOSIS
- 1350 DID NOT MEET STRESS CRITERIA AS DIRECTED BY CORE FACILITY DCRI
- 1396 DID NOT UNDERGO CTA

INVASIVE GROUP

- 2588 PATIENTS
- 95.6% UNDERWENT ANGIOGRAPHY
- 79.4% HAD REVASCULARIZATION PCI OR CABG
- THE REST WERE TREATED LIKE THE CONSERVATIVE GROUP
- TOTAL NUMBER OF PROCEDURES WERE 5337

CONSERVATIVE GROUP

- 2591 PATIENTS
- 25.7% ENDED UP WITH ANGIOGRAPHY
- 21% ENDED UP WITH SOME FORM OF REVASCULARIZATION
- TOTAL PROCEDURES 1506

BASELINE CHARACTERISTICS

- EQUAL ACROSS BOTH GROUPS
- 66% WHITE
- 29% ASIAN
- <1% INDIGENOUS PEOPLE
- MEAN EF 62%
- BASELINE LDL 83 (64 AT END OF TRIAL)

OUTCOMES

- AT 3.2 YEARS 318 EVENTS IN INVASIVE GROUP, 352 CONSERVATIVE
- AT 5 YEARS, 16.4% MACE FOR INVASIVE AND 18.2% CONSERVATIVE
- 5 YEARS 145 DEATHS IN INVASIVE AND 144 DEATHS IN CONSERVATIVE GROUP

MY PROBLEMS WITH THIS STUDY

- OVERALL A LOW RISK GROUP BY OUR STANDARDS
- NOT CONSISTENT WITH OUR POPULATION BASE
- 20% OF INVASIVE GROUP DID NOT RECEIVE ANYTHING BUT MEDICAL THERAPY
- 20% OF CONSERVATIVE GROUP RECEIVED NONRANDOMIZED TREATMENT
- ANTIPLATELET THERAPY OR STENT TYPES NOT CONTROLLED
- THEY COUNTED PROCEEDURAL MI'S AS MACE

PROBLEMS

- WE DO NOT HAVE THE ABILITY TO DO CTA ON THESE PATIENT GROUPS TO R/O NONOBSTRUCTIVE DISEASE OR LEFT MAIN
- FOLLOWUP AND COMPLIANCE WITH MEDICAL TREATMENT FOR BOTH GROUPS WAS 98%!!!
- WHO EVER SEES THAT
- NO PATIENTS WITH CKD IN THESE GROUPS...SO

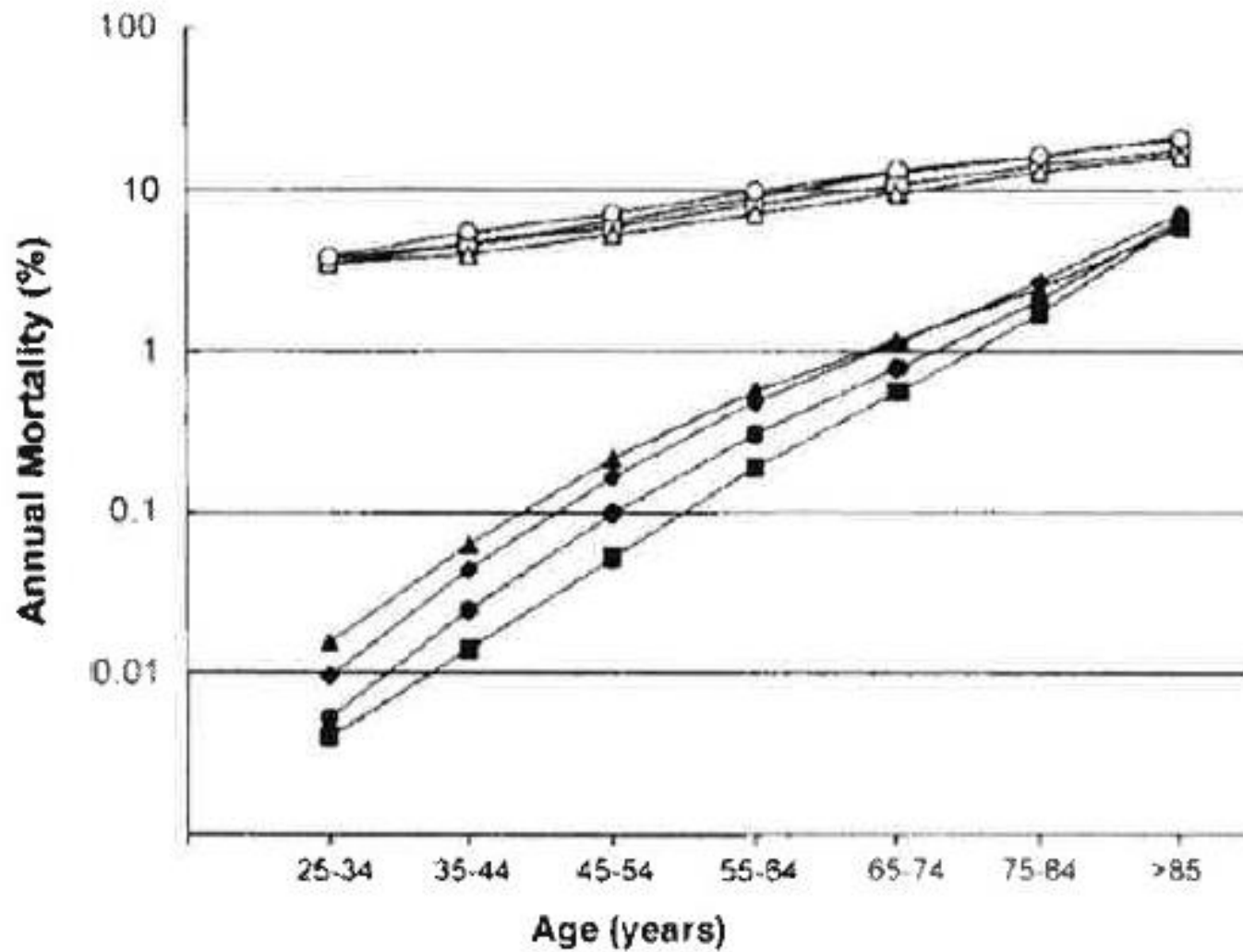


Figure 1 from Foley et al, AJKD Supplements, 1998

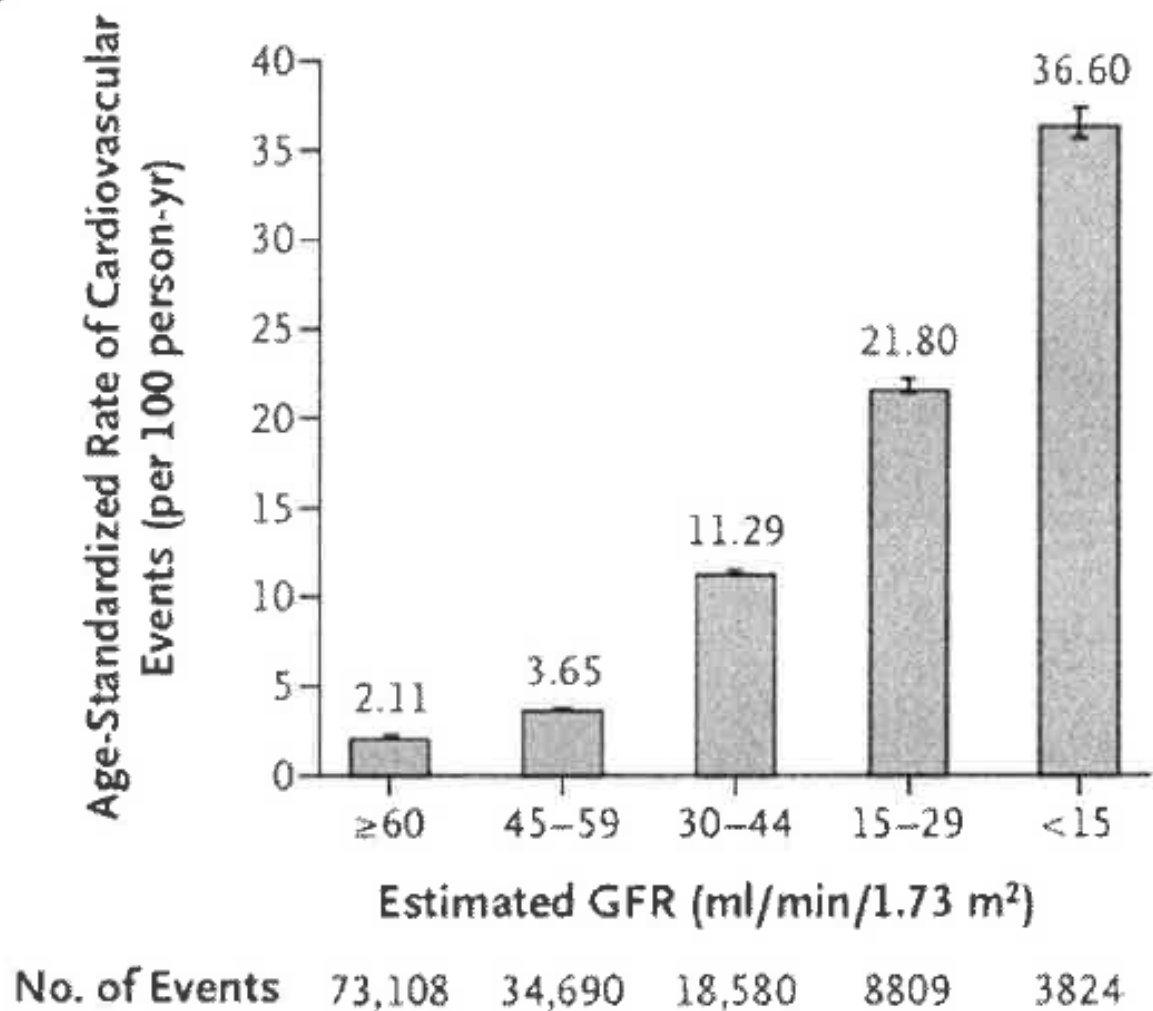
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Figure 1b from Go et al, NEJM 2004

ISCHEMIA - CKD

- 777 PATIENTS
- MODERATE OR SEVERE ISCHEMIA ON STRESS TESTING
- FOLLOWUP 2.2 YEARS
- AGE > 21
- GFR < 30 ML/MIN OR HEMODIALYSIS
- STABLE PATIENTS WITH NO RECENT CV EVENTS

EXCLUSION CRITERIA

- EF < 35%
- LEFT MAIN > 50%
- NYHA CLASS III OR IV CHF
- LIFE EXPECTANCY PREDICTED TO BE LESS THAN THE TRIAL DURATION (RATHER SUBJECTIVE)

INVASIVE ARM

- ANGIOGRAPHY WITHIN 30 DAYS
- NO CTA SECONDARY TO LOW GFR
- OMT (OPTIMAL MEDICAL THERAPY)
- REVASCULARIZATION IF CLINICALLY APPROPRIATE
- PCI OR CABG ACCORDING TO LOCAL HEART TEAM

CONSERVATIVE GROUP

- OMT ALONE
- ANGIOGRAPHY RESTRICTED TO THOSE FAILING OMT
- FAILURE DEFINED AS THOSE WITH ACS, NEW CHF, CARDIAC ARREST OR SEVERE ANGINA

OPTIMAL MEDICAL THERAPY

- SMOKING CESSATION PROGRAM
- PHYSICAL ACTIVITY > 30 MINUTES 5 DAYS A WEEK
- BP <130/80
- LDL < 70 MG/DL
- BMI < 25
- A1C < 8%
- ASPIRIN OR P2Y12 INHIBITOR

OUTCOMES EVALUATED

- PRIMARY: DEATH OR NONFATAL MI
- SECONDARY: COMPOSITE OF DEATH, NONFATAL MI, HOSPITALIZATION FOR ACS, CHF, CARDIAC ARREST, ANGINA RELATED QUALITY OF LIFE SCORE. SEATTLE
- SAFETY OUTCOME: INITIATION OF DIALYSIS OR COMBINATION OF DIALYSIS OR DEATH

CHARACTERISTICS OF PATIENTS

- MEAN AGE 63
- 57% DIABETES
- 53% HEMODIALYSIS PATIENTS
- MEDIAN GFR 23 ML/MIN/1.73M2
- 92% HYPERTENSION
- 64% WHITE
- 25% ASIAN

INVASIVE GROUP

- 85% UNDERWENT ANGIOGRAPHY
- 33% OF CONSERVATIVE GROUP UNDERWENT ANGIO AND 25% HAD REVASCULARIZATION
- 50% UNDERWENT REVASCULARIZATION
- 85% HAD PCI
- 15% HAD CABG DESPITE 57% WITH DM

OUTCOMES

- NO DIFFERENCE BETWEEN THE TWO GROUPS
- HIGHER INCIDENCE OF STROKE IN INVASIVE GROUP
- HIGHER INCIDENCE OF NEW DIALYSIS IN INVASIVE GROUP DESPITE MEASURES
- STUDY SHOULD HAVE LASTED LONGER
- LESS THAN HALF OF PATIENTS HAD NO ANGINA JUST ISCHEMIA ON STRESS TESTING

ISAR-REACT-5

- MULTICENTER
- RANDOMIZED
- OPEN LABEL TRIAL
- ACS STEMI OR NONSTEMI
- EVALUATION OF DEATH, MI, STROKE IN 1 YEAR
- SECONDARY SAFETY END POINT WAS BLEEDING

PROTOCOL

- TICAGRELOR LOADING BEFORE CATH VRS
PRASUGREL LOADING AFTER RESULTS OF CATH
KNOWN TO MIMIC MAJOR TRIALS
- CHARACTERISTICS AT BASELINE SIMILAR
- 1:1 RANDOMIZATION
- 84% IN BOTH GROUPS RECEIVED PCI WITH CABG IN
2% MEDICAL THERAPY 14%
- 41% ENROLLED WITH STEMI

OUTCOMES

- DEATH TICAGRELOR 4.5% VRS 3.7%
- MI 4.8% VRS 3.0%
- CVA 1.1% VRS 1.0%
- BARC SCORE BLEEDING 5.4% VRS 4.8%
- DEFINITE OR PROBABLE STENT THROMBOSIS 1.3% VRS 1.0%
- TOTAL 9.3% IN TICAGRELOR GROUP AND 6.9% IN PRASUGREL GROUP

COMPLIANCE

- AT 1 YEAR FOLLOW UP
- 243/1602 PATIENTS STOPPED TICAGRELOR AT AN AVERAGE OF 84 DAYS
- 199/1596 STOPPED PRASUGREL AT AVERAGE OF 109 DAYS
- 44 PATIENTS WITH TICAGRELOR HAS DYSPNEA (ADENOSINE EFFECT) ONLY 1 WITH PRASUGREL

CONSIDERATION FOR PATIENTS IN OUR REGION

- TICAGRELOR IS BRAND NAME AND PRASUGREL IS NOT COST \$\$\$
- PRASUGREL GIVEN POST CATH SO LESS PROCEDURAL BLEEDING?
- RELATIVELY FEW THROMBOTIC EVENTS AFTER 90 DAYS EVEN AFTER MANY PATIENTS STOPPED DAPT ATTRIBUTABLE TO NEWER GENERATION STENTS

EVAPORATE TRIAL

- REDUCE-IT SHOWED VASCEPA REDUCED TOTAL ISCHEMIC EVENTS AS AN ADJUNCT TO STATIN THERAPY BY 31%
- THIS WAS A SURPRISE AND SEEMED TOTALLY OUT OF PROPORTION TO TG LOWERING EFFECT
- WAS BENEFICIAL EVEN IN THOSE WITHOUT ELEVATED TRIGYCERIDES
- THEREFORE: EVAPORATE

EVAPORATE

- 2GRAMS TWICE DAILY OF PURIFIED EPA VRS
PLACEBO
- 80 PATIENTS WITH TG 135-499
- LDL WAS 40-115
- ALL PATIENTS ON MAXIMALLY TOLERATED STATIN
- MINERAL OIL PLACEBO
- PRIMARY ENDPOINT WAS CHANGE IN LOW
ATTENUATION PLAQUE AT 18 MONTHS BY CCTA

RESULTS

- TOTAL PLAQUE -9% INTREATMENT GROUP VRS +11% IN PLACEBO
- NONCALCIFIED PLAQUE -19% VRS + 9%
- FIBROUS PLAQUE -20% VRS +1%
- LOW ATTENUATED PLAQUE -17% VERSUS + 109%
- NO SIGNIFICANT SERIAL CHANGE IN TG
- MECHANISM LIKELY SECONDARY TO INHIBITING PLATELET AGGREGATION AND FOAM CELL FORMATION

BEMPEDOIC ACID

NEJM 3/14/19

- SAFETY AND EFFICACY OF BA TO REDUCE LDL CHOLESTEROL (CLEAR HARMONY TRIAL)
- INHIBITOR OF ATP CITRATE LYASE AN UPSTREAM ENZYME ON THE CHOLESTEROL SYNTHESIS PATHWAY
- PRODRUG ACTIVATED BY ACY CoA SYNTHETASE 1 PRESENT ONLY IN THE LIVER NOT PERIPHERAL TISSUES

PROTOCOL

- 52 WEEKS OF ORAL TREATMENT
- MAX TOLERATED STATIN ALONE OR IN COMBINATION WITH OTHER MEDS
- LDL BEFORE TREATMENT > 70, IF LDL >170 PCSK9 ADDED
- PRIMARY OUTCOME WAS SAFETY
- SECONDARY: ABILITY TO LOWER LDL, NONHDL, TOTAL CHOLESTEROL, APO-B, AND hsCRP

BASELINE

- 1950 PATIENTS
- 2:1 RANDOMIZATION
- 98% WITH CAD
- 3.8% WITH FAMILIAL
- LDL AVERAGE 102, HDL 49, hsCRP 1.5
- 98% ON STATIN
- 7.8% ZETIA AND 3.6% FIBRATES

SAFETY

- MYALGIAS 6% SAME AS PLACEBO
- MUSCLE DISORDER LEADING TO DISCONTINUATION
2.1 % VRS 1.9%
- ELEVATED URIC ACID 1.2% VRS 0.3%
- 15 DEATHS NON FELT RELATED TO THE DRUG

RESULTS

- LDL DOWN 16.5%
- NON HDL – 11.9%
- TOTAL CHOL - 11.1%
- APO-B -8.6%
- hsCRP DOWN 22.4%
- RESULTS LASTED FROM WEEK 8 TO WEEK 52
- NOW AVAILABLE BY ITSELF OR IN COMBINATION WITH EZETIMIDE

INCLISIRIN

- STUDIES PERFORMED ORION 8,9,10,11
- SMALL iMRNA THERAPY
- INTERFERES WITH PCSK9 PRODUCTION IN THE CELL
- LEADING TO MARKED REDUCTIONS IN PRODUCTION AND THUS LDL RECEPTOR
- MARKEDLY REDUCES LDL
- LONG ACTING ONLY GIVEN TWICE A YEAR AS AN INJECTION

ORION 10,11

- 284 MG SQ Q 6 MONTHS VRS PLACEBO
- PRIMARY ENDPOINT AT DAY 510, AND CHANGE FROM DAY 90 TO DAY 540
- ORION 10 1561 PTS MEAN LDL REDUCTION 52.3%
- ORION 11 1617 49.9% REDUCTION IN LDL
- 90% ON MAXIMALLY TOLERATED STATIN 10% ZETIA
- FEW < 3% ANTIBODIES AGAINST THE DRUG

ORION 9

- FAMILIAL HYPERCHOLESTEROLEMIA THERAPY
- 90% OF CASES ARE VARIANTS IN THE GENE CODING FOR LDL RECEPTORS. MANY TYPES
- ,10% RELATED TO GENES CODING FOR APO-B OR PCSK9
- MAX TOLERATED STATIN PLUS ZETIA WITH INJECTIONS ON DAY 1, 90, 270 AND 450

ORION 9

- 482 RANDOMIZED 1:1
- AVERAGE AGE 56
- 47% MEN
- 94% WHITE
- LDL WAS 153
- RESULTS: 65% LESS THAN 100 MG/DL, AND 41% LESS THAN 70
- EQUAL IN BENEFIT TO PCSK9 INHIBITORS WITH 4 INJECTIONS RATHER THAN 38!!

ORION 9

- WAS EQUALLY BENEFICIAL IN ALL TYPES OF GENE VARIANTS
- WELL TOLERATED WITH FEW SITE REACTIONS
- 39.7% REDUCTION IN LDL
- WITH AN 8.2% INCREASE IN THE PLACEBO GROUP SO A 47.9% DIFFERENCE!!
- THE NEXT GREAT UNAFFORDABLE DRUG THAT INSURANCE COMPANIES WON'T LET US USE!

STATINS IN THE ELDERLY

- JAMA 2020;324(1)68-78
- RETROSPECTIVE TRIAL
- 326,981 VETERANS AVERAGE AGE 81
- 97% MEN AND 91% WHITE
- FOLLOWED 6.8 YEARS WITH 209,902 DEATHS AND 52,296 CV DEATHS

STATINS IN THE ELDERLY

- 78.7 DEATHS PER 1000 PERSON-YEARS IN STATIN GROUP
- 98.2 DEATHS PER 1000 PERSON-YEARS IN NONSTATIN GROUP
- 25% REDUCTION IN EVENTS
- SIMILAR RATES SEEN IN THE ABOVE 90 AGE GROUP

OTHER GOOD READING

- DAPA-HF
- ANYTHING AT ALL RELATED TO THE SGLPT INHIBITORS
- THE NEXT GREAT KIDNEY, HEART, DIABETES MEDICATION
- APPEARS TO BE A GROUP EFFECT WITH NEW DRUGS ON THE HORIZON