"Why CREST2 May Not Provide Any Valid Answers Because of Bad Patient Selection in CREST2 & Because BMT May Not Be Optimal Without GLP1-Agonists"

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Disclosures

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The Carotid Revascularization and Medical Management for Asymptomatic Carotid Stenosis Study

CREST-2

Funded by the NIH

2-Arms:
BMT+CEA
(complete)
BMT+ CAS
(complete)

Two Companion Registries:
C2R,
CREST-H

Purpose

Are CEA & stenting as good as consistent, intensive modern medical therapy?

A lingering but critically important question

cases within 5 years

yrs old, SSR
with a
stenosis ≥ 70%
by angio*

Locations

USA, Canada, Spain, Israel

Enrollment

144 CREST-2 Centers have enrolled *2187* out of a target of *2480* patients

**30+ Exclusion criteria, not including the additional conditions specific to CAS and/or CEA*

Potential Limitation: Lesion Severity

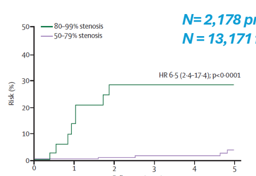
LACK OF EQUIPOISE:
- **Stenoses ≥ 80% may be excluded**
- **Rapidly progressing stenoses may be excluded**

UNDER-REPRESENTATION **OF LESIONS THAT TRULY WARRANT REVASCULARIZATION?**

Systematic Review & Meta-Analysis

Professor of Neurology, Director of the Stroke Prevention Research Unit (SPRU) at the University of Oxford

Profile
Peter Rothwell: aspirin(g) physician with a little stroke of genius



N= 2,178 prospective from OxVasc Registry
N = 13,171 from RCTs

Contemporary BMT:
5-yr risk for ≥ 80% stenosis is 18.3%

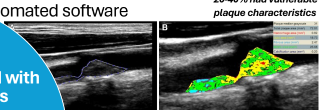
Howard PJ, Gaziaano L, Rothwell PM, on behalf of the Oxford Vascular Study. Risk of stroke in relation to degree of asymptomatic carotid stenosis: a population-based cohort study, systematic review and meta-analysis, Lancet Neurology 2021;20:193-202

CREST2 Stenosis Grade & Plaque Characteristics

- DUS manually ... automated software
  - *Sten...*
  - *In...*

HOWEVER,
- **PSV poorly correlated with plaque characteristics**
- **Only 503 patients (21% of CREST2)**
- **Not routine practice**
- **? Representative sample**

20-40% had vulnerable plaque characteristics



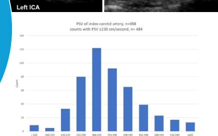


Fig 3. Distribution of duplex ultrasound (DUS) peak systolic velocity (*PSV*) measurements for study population.

Lal BK, Jreij G, Crencik M et al, Carotid Plaque Characteristics in the CREST2 Trial, JVS-Vascular Insights 2024;2:100134

Will CREST-2 Stand The Test of Time?

- Stroke rates low with CEA & CAS in this population
  - ACT1
  - CREST2R
- Annualized stroke rates low on intensive medical Rx
  - Margin of benefit narrow
  - Statistical difference hard to achieve
- *Any game-changing paradigm (on either side) may shift the balance*

- Asymptomatic, Standard Risk Population
- 3:1 randomization (CAS:CEA)

ACT-1

	CAS	CEA	p value
1 yr S/D/MI	3.8%	3.4%	0.01
30d S/D/MI	3.3%	2.6%	0.6
30d All Stroke	2.8%	1.4%	0.23

OBSOLETE AT TIME OF REPORTING?
- No GLP1-agonists
- TCAR not included

Rosenfield K, Matsumura JS, Chaturvedi S, et al; ACT I Investigators. Randomized Trial of Stent versus Surgery for Asymptomatic Carotid Stenosis. N Engl J Med. 2016 Mar 17;374(11):1011-20

Stroke Risk Modification

Type II Diabetics: GLP1-agonist class effect, protection against ischemic stroke *(in conjunction with lifestyle modifications)*[1]
- Meta-analysis, 8 RCTs
- GP1-agonist vs. placebo > 60K patients
- 27% reduction total stroke (p=0.005)
- 27% reduction in ischemic stroke (p=0.008)

Type II Diabetics: GLP1-Agonist Fewer 1st Strokes[2]
- Post Hoc Analysis of the Randomized SUSTAIN 6 (injection) & PIONEER 6 (oral formulation) trials, N=6480
- Semaglutide reduced the incidence of any first stroke compared with placebo (0.8 vs. 1.1 events/100 PYO; hazard ratio [HR]: 0.68; 95% CI: 0.46–1.00; P = 0.048)

Stroke survivors: GLP1-Agonists & SGLT2 inhibitors[3]
- 3-year risk of S/D/MI
- N >7,000
- Adults taking either a GLP-1 or an SGLT2 had a 74% lower risk of death & an 84% lower risk of having an MI
- Adults who were taking an SGLT2 were also at a 67% lower risk of having another stroke
- Risk reduction persisted after matching for age, sex, smoking status, HT, Type 2 diabetes status, PAD, hyperlipidemia, CKD & a history of MI or HF

1. Wei J, Yang B, Wang R, Yu H, Wang Y, Wang L, Zhang X. Risk of stroke and retinopathy during GLP-1 receptor agonist cardiovascular outcome trials: An eight RCTs meta-analysis. Front Endocrinol (Lausanne). 2022 Dec 5;13:1007880.
2. Strain WD, Frenkel O, James MA, Leitar LA, Rasmussen S, Rothwell PM, Ripa MS, Truelsen TC, Husain M. Effects of Semaglutide on Stroke Subtypes in Type 2 Diabetes: Post Hoc Analysis of the Randomized SUSTAIN 6 and PIONEER 6. Randomized Controlled Trial. Stroke 2022 Sep;53(9):2749-2757. doi: 10.1161/STROKEAHA.121.037775. Epub 2022 May 18.
3. Shaffeh MA, American Heart Association Scientific Sessions 2024, Abstract 4148007, November 11th 2024

Estimated10-yr population-based CV risk reduction (GLP-1 Agonists In Obese Non-Diabetics)

- "STEP1" RCT eligibility criteria applied to NHANES data (2015-2018)
- Estimated 10-year CVD risk (BMI-based Framingham CVD scores)
- Difference in estimated risks +/- semaglutide x eligible NHANES weighted population = ***PREVENTABLE CVD EVENTS***
  - *Among those without CVD, estimated 10-year CVD risks were 10.15% "before" and 8.34% "after" semaglutide "treatment"*
  - *1.81% absolute (and 17.8% relative) risk reduction*
  - *Translating to 1.50 million preventable CVD events over 10 years*

Wong ND, Karthikeyan H, Fan W. US Population Eligibility and Estimated Impact of Semaglutide Treatment on Obesity Prevalence and Cardiovascular Disease Events Cardiovasc Drugs Ther 2023 Aug 14. doi: 10.1007/s10557-023-07488-3. Online ahead of print.

Conclusion:

- Stratify the outcomes of CREST2 by degree of stenosis
  - Good representation of significant/rapidly progressing stenoses?
- GLP-1 Agonists (& to some extent SGLT2 Inhibitors):

***GAME CHANGER* or emperor's new clothes?**

- The side effect profile is ***not*** benign

GERD	Hypoglycemia	Dizziness
Gastritis	Diabetic retinopathy	Dysgeusia
Nausea	Pancreatitis†	Delayed absorption of oral medications‡
Gastroparesis*	Acute kidney injury	Depression
Cyclic vomiting syndrome	Thyroid C-Cell Cancer††	Suicidal thoughts
Anesthesia risks**	Tachycardia	Weight loss in unintended areas ("Ozempic® face")
Diarrhea/dehydration	Hospitalization for heart failure	Fat-free mass loss¥
Cholelithiasis	Fatigue	

Lingvay I, McGowan BM, Orsi TK, Rosenstock J, Wadden TA, Wharton S, Yokote K, Kushner RF, and STEP 1 Study Group Weight regain and cardiometabolic effects after withdrawal of semaglutide: The STEP 1 trial extension. Stirling JPH, Batterham RL, Davies M, Van Gaal LF, Kandler K, Konakli K, Diabetes Obes Metab. 2022 Aug; 24(8): 1553–1564. Published online 2022 May 19. doi: 10.1111/dom.14722.