TCTAP & APVALVES 2020

# Left Main PCI vs CABG:

# Cardiac Surgeon Perspective

**David P Taggart** MD PhD FRCS FESC
Professor of Cardiovascular Surgery, University of Oxford

Conflicts of Interest:

(i) Clinical: Cardiac Surgeon
(ii) Chairman of Surgical Ctte of EXCEL but withdrew from final NEJM publication in 2019
(iii) Commercial: Consultant to Medistim, Medtronic, VGS

# CABG vs PCI DATA: 4 Key 'Rules' For Interpreting Data

**(i) Are TRIAL patients typical of real practice (CAD severity) ?**

✖ No: usually very selected (< 10%) patients with less severe CAD

✔ **Underestimates the benefit of CABG in routine practice**

**(ii) Duration of follow-up ?**

✖ Must be a **minimum** of 5 years (ideally 10 years as in the ART)

✔ **Increasing length of follow-up = increasing benefit of CABG**

**(iii) Use of Guideline Directed Medical Therapy (GDMT) ?**

✖ Always **SIGNIFICANTLY** inferior in CABG vs PCI patients

✔ **CABG + GDMT: then even greater benefits over PCI**

**(iv) Examine Data/Results Before Reading Text** (pro PCI bias)

✖ Why ?: text often contradicts what the ACTUAL DATA shows

✔ **Data shows superiority of CABG for Survival/MI/Recasc**

## Multi-Vessel Disease (No Left Main):

## CABG is a Clear Winner for All (Any Level of SYNTAX Score):

## and Especially in DM

## Isolated Left Main Disease (Very Uncommon <5%) !

## (Up to 90% of Patients also have multi-vessel disease)

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doi:10.1016/j.jacc.2007.09.067

STATE-OF-THE-ART PAPER AND COMMENTARY

# Revascularization for Unprotected Left Main Stem Coronary Artery Stenosis

## Stenting or Surgery

David P. Taggart, MD (Hons), PhD, FRCS,* Sanjay Kaul, MD, FACC,†
William E. Boden, MD, FACC,‡ T. Bruce Ferguson, Jr, MD, FACC,§
Robert A. Guyton, MD, FACC,¶ Michael J. Mack, MD,# Paul T. Sergeant, MD, PhD,††
Richard J. Shemin, MD, FACC,** Peter K. Smith, MD, FACC,‖
Salim Yusuf, DPhil, FRCPC, FRSC, FACC‡‡

*Oxford, United Kingdom; Los Angeles, California; Buffalo, New York; Greenville and Durham,*

O<90% of LMS are distal/bifurcation (high risk of restenosis)
(confirmed in EXCEL where 85% distal LM)
O<90% have multivessel CAD (CABG already offers survival benefit)

spite very little high-quality data to inform clinical practice. We herein: 1) evaluate the current evidence in support of the use of percutaneous revascularization for unprotected LMS; 2) assess the underlying justification for randomized controlled trials of stenting versus surgery for unprotected LMS; and 3) examine the optimum approach to informed consent. We conclude that CABG should indeed remain the preferred revascularization treatment in good surgical candidates with unprotected LMS stenosis. (J Am Coll Cardiol 2008;51:885–92) © 2008 by the American College of Cardiology Foundation

# Extraordinary Contribution of SJ Park and Colleagues to Left Main Disease !

The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 APRIL 24, 2008 VOL. 358 NO. 17

## Stents versus Coronary-Artery Bypass Grafting for Left Main Coronary Artery Disease

Ki Bae Seung, M.D., Duk-Woo Park, M.D., Young-Hak Kim, M.D., Seung-Whan Lee, M.D., Cheol Whan Lee, M.D., Myeong-Ki Hong, M.D., Seong-Wook Park, M.D., Sung-Cheol Yun, Ph.D., Hyeon-Cheol Gwon, M.D., Myung-Ho Jeong, M.D., Yangsoo Jang, M.D., Hyo-Soo Kim, M.D., Pum Joon Kim, M.D., In-Whan Seong, M.D., Hun Sik Park, M.D., Taehoon Ahn, M.D., In-Ho Chae, M.D., Seung-Jea Tahk, M.D., Wook-Sung Chung, M.D., and Seung-Jung Park, M.D.

## MAIN-COMPARE Registry: PCI vs CABG in 2240 LM Disease Patients @ 3 yr/10 yr

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

## Randomized Trial of Stents versus Bypass Surgery for Left Main Coronary Artery Disease

Seung-Jung Park, M.D., Young-Hak Kim, M.D., Duk-Woo Park, M.D.,

PRECOMBAT: RCT 600 patients

Follow-up 2yr (NEJM 2011), 5 yr (JACC 2015), 10 yr (CIRC 2020)

Circulation

ORIGINAL RESEARCH ARTICLE

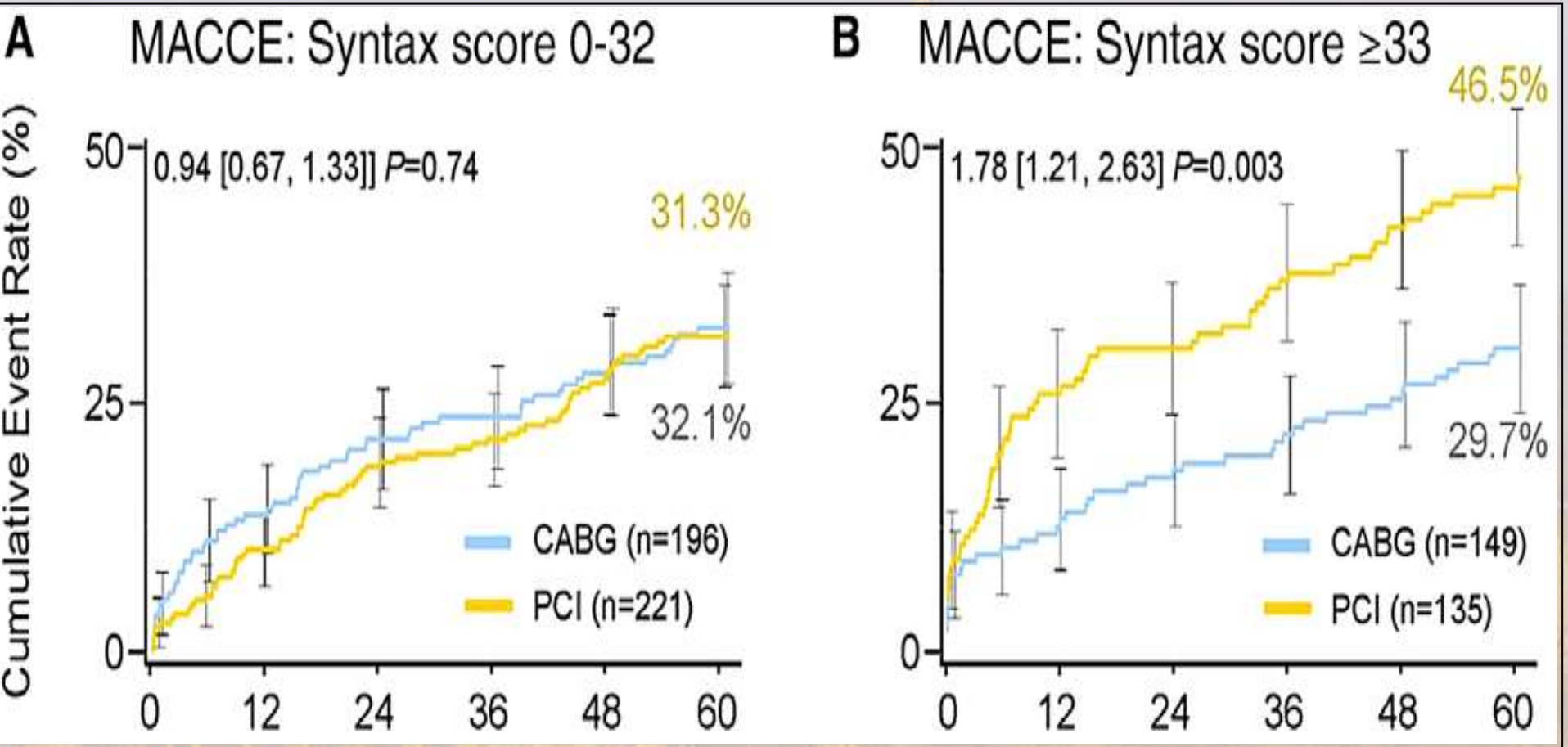
## Ten-Year Outcomes After Drug-Eluting Stents Versus Coronary Artery Bypass Grafting for Left Main Coronary Disease

### Extended Follow-Up of the PRECOMBAT Trial

Editorial, see p 1447

Duk-Woo Park, MD*
Jung-Min Ahn, MD*

EXCEL LEFT MAIN Trial
Underpinned by SYNTAX trial
705 RCT patients (1 and 5 years)
NEJM 2009, CIRC 2014




① Accelerating Divergence of MACCE Curves in Favour of CABG in >32
② Used to define patients in the EXCEL trial (ie Syntax Scores <33)
③ CABG: Competitive flow if low SYNTAX scores ie less proximal CAD ??

# Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease

[NEJM 2019]

G.W. Stone, A.P. Kappetein, J.F. Sabik, S.J. Pocock, M.-C. Morice, J. Puskas, D.E. Kandzari, D. Karmpaliotis, W.M. Brown III, N.J. Lembo, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P.E. Buszman, A. Bochenek, E. Schampaert, P. Pagé, R. Modolo, J. Gregson, C.A. Simonton, R. Mehran, I. Kosmidou, P. Généreux, A. Crowley, O. Dressler, and P.W. Serruys, for the EXCEL Trial Investigators*

- **SELECTED** LEFT MAIN DISEASE: SYNTAX SCORES <33
- 1905 patients (trial stopped early vs 2600 planned patients)
- MEAN AGE 66: (life expectancy of 15-20 years)
- Primary outcome Composite: Death, MI, Stroke (NOT Revasc)

36/37 Authors (after DT withdrew) *

# EXCEL: The Controversy

- 3 major societies of cardiothoracic surgery (EACTS, AATS, STS) demand **INDEPENDENT** re-analysis of the results
- Both CRF (who conducted the trial) and the NEJM announced respective investigations into the conduct and reporting of EXCEL (both remain unreported to date)
- BBC 'Newsnight' produced two reports regarding failure of EXCEL to report Myocardial Infarction Data and the Concerns of the DSMB

## Four Major Concerns in EXCEL 5-Year Analysis:

1. Changed Statistical Analysis: Non-Inferiority (3 ys) to Superiority (5 yr)
2. Interpretation of the Mortality Data
3. Persistent Failure to Publish Protocol Specified MI Data
4. Failure to Share Trial Data

# Excel: The Facts

1) The largest and most definitive trial of PCI vs CABG in LM disease (4 PI: GWS, APK, PWS, JS: enormous credit for driving this pivotal and seminal landmark trial !)

2) Academic: I was Chairman of the Surgical Committee of the EXCEL Trial during the design and recruitment phase

3) Oxford: 2nd largest recruiter of EXCEL patients worldwide (n=100), (demonstrating real commitment of Oxford Cardiologist/Surgeons !)

4) I withdrew my authorship from the final NEJM manuscript (2019) over INTERPRETATION of the data

5) **There was NO attempt in the EXCEL trial to manipulate/distort the data that was actually presented**

6) **BUT, there was a failure to present protocol specified data that was vitally important to the 'true' interpretation of the EXCEL trial**

# CONCERN 1. EXCEL: 'Statistical Trickery'

ESTABLISHED IN 1812 DECEMBER 8, 2016 VOL. 375 NO. 23

## Everolimus-Eluting Stents or Bypass Surgery for Left Main Coronary Artery Disease

G.W. Stone, J.F. Sabik, P.W. Serruys, C.A. Simonton, P. Généreux, J. Puskas, D.E. Kandzari, M.-C. Morice, N. Lembo, W.M. Brown III, D.P. Taggart, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P. Buszman, A. Bochenek, E. Schampaert, P. Pagé, O. Dressler, I. Kosmidou, R. Mehran, S.J. Pocock, and A.P. Kappetein, for the EXCEL Trial Investigators*

Primary outcome at 3 years: **Non-Inferiority** upper margin 4.2%

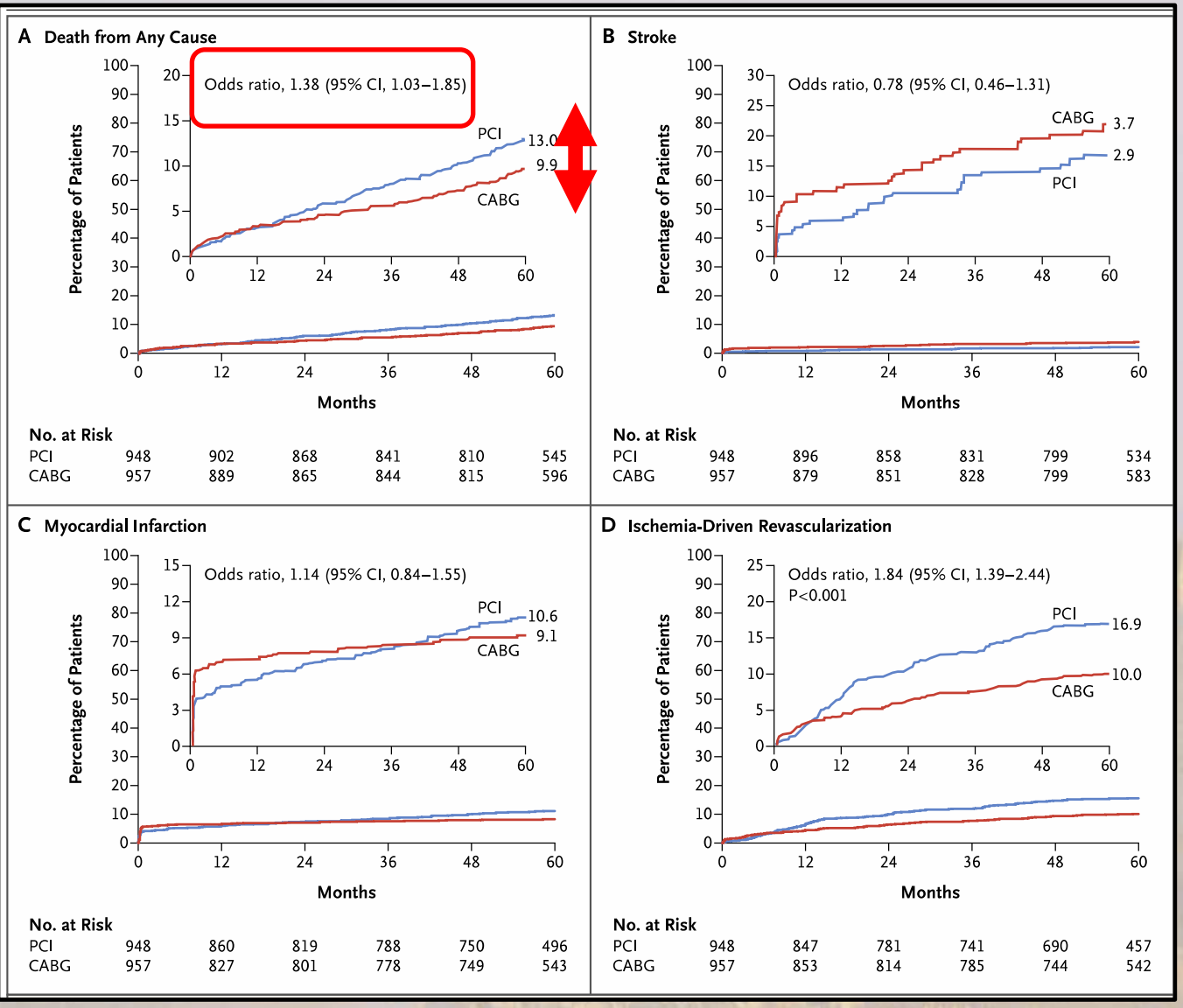
## Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease

G.W. Stone, A.P. Kappetein, J.F. Sabik, S.J. Pocock, M.-C. Morice, J. Puskas, D.E. Kandzari, D. Karmpaliotis, W.M. Brown III, N.J. Lembo, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P.E. Buszman, A. Bochenek, E. Schampaert, P. Pagé, R. Modolo, J. Gregson, C.A. Simonton, R. Mehran, I. Kosmidou, P. Généreux, A. Crowley, O. Dressler, and P.W. Serruys, for the EXCEL Trial Investigators*

Without discussion or explanation Primary outcome at 5 years: '**Superiority**': 2.8%: 95% CI -0.9% to 6.5%: p=0.13

Were the statisticians and NEJM asleep ?

# CONCERN 2: EXCEL: 5 YEARS 'Clinical Reality'




Patients (age 66 yr, with low/ intermediate severity LM disease)

- Death (38% increase),
- Non-procedural MI (ie real MI),
- Repeat Revasc

are all accelerating in the PCI group.

**CONCLUSIONS** In patients with left main coronary artery disease of low or intermediate anatomical complexity, there was no significant difference between PCI and CABG with respect to the rate of the composite outcome of death, stroke, or myocardial infarction at 5 years. (Funded by Abbott Vascular)

**Table 2. Primary and Secondary Outcomes over Three Periods.***

| Variable | PCI | | CABG | | Hazard Ratio (95% CI) |
|---|---|---|---|---|---|
| | Events | Event Rate | Events | Event Rate | |
| | *no./no. of patients* | % | *no./no. of patients* | % | |
| **Outcomes at 30 days** | | | | | |
| Death, stroke, or myocardial infarction | 46/948 | 4.9 | 75/957 | 8.0 | 0.61 (0.42–0.88) |
| Death | 9/948 | 1.0 | 10/957 | 1.1 | 0.90 (0.37–2.21) |
| Stroke | 6/948 | 0.6 | 12/957 | 1.3 | 0.50 (0.19–1.32) |
| Myocardial infarction | 37/948 | 3.9 | 59/957 | 6.3 | 0.63 (0.42–0.94) |
| Death, stroke, myocardial infarction, or ischemia-driven revascularization | 46/948 | 4.9 | 80/957 | 8.5 | 0.57 (0.40–0.82) |
| Ischemia-driven revascularization | 6/948 | 0.6 | 13/957 | 1.4 | 0.46 (0.17–1.21) |
| Definite stent thrombosis or symptomatic graft stenosis or occlusion | 3/948 | 0.3 | 11/957 | 1.2 | 0.27 (0.08–0.97) |
| **Outcomes from 30 days to 1 yr** | | | | | |
| Death, stroke, or myocardial infarction | 38/948 | 4.1 | 35/957 | 3.8 | 1.07 (0.68–1.70) |
| Death | 22/948 | 2.4 | 23/957 | 2.5 | 0.94 (0.53–1.69) |
| Stroke | 5/948 | 0.5 | 7/957 | 0.8 | 0.71 (0.22–2.23) |
| Myocardial infarction | 16/948 | 1.7 | 10/957 | 1.1 | 1.58 (0.72–3.48) |
| Death, stroke, myocardial infarction, or ischemia-driven revascularization | 83/948 | 8.9 | 56/957 | 6.1 | 1.48 (1.05–2.07) |
| Ischemia-driven revascularization | 59/948 | 6.4 | 28/957 | 3.1 | 2.10 (1.34– 3.30) |
| Definite stent thrombosis or symptomatic graft stenosis or occlusion | 0/948 | 0 | 22/957 | 2.4 | — |
| **Outcomes from 1 yr to 5 yr** | | | | | |
| Death, stroke, or myocardial infarction | 133/933 | 15.1 | 83/929 | 9.7 | 1.61 (1.23–2.12) |
| Death | 88/933 | 10.0 | 56/929 | 6.6 | 1.57 (1.12–2.19) |
| Stroke | 16/933 | 1.9 | 15/929 | 1.8 | 1.06 (0.52–2.15) |
| Myocardial infarction | 43/933 | 5.1 | 20/929 | 2.4 | 2.16 (1.27–3.67) |
| Death, stroke, myocardial infarction, or ischemia-driven revascularization | 198/933 | 22.4 | 118/929 | 13.8 | 1.74 (1.38–2.18) |
| Ischemia-driven revascularization | 100/933 | 11.6 | 49/929 | 5.8 | 2.10 (1.49–2.95) |
| Definite stent thrombosis or symptomatic graft stenosis or occlusion | 7/933 | 0.8 | 25/929 | 3.0 | 0.28 (0.12–0.64) |

# Primary and Secondary Outcomes over 3 Periods

## 0-30 DAYS

**No difference:**
**Death, Stroke, Revasc**
CABG: MI higher using **new biochemical definition**

## 30 DAYS-1Year

**No difference:**
**Death, Stroke, MI,**
PCI: Revasc higher

## 1-5 Years

PCI: Large Increase:
Death, MI, Revasc
**(no difference in stroke)**

CONCLUSION: 'No Difference' ?????

# CONCERN 3: Failure to Publish Protocol Defined MI

**EXCEL Protocol SPECIFIED reporting of BOTH a new biochemical definition of procedural MI (SCAI), introduced by the PI, and the standard definition (UDMI).**

- **VITAL 'safety check' to compare two definitions (i) in EXCEL and (ii) other studies;**
- **BUT only the new definition, that drove the composite end point was reported !**

**UDMI data (presented on BBC) shows far higher rate of MI in PCI group !**

**EXCEL Clinical Trial Protocol Version 4.0: 22nd July 2011 [NEJM 2019]**
**'Protocol Defined MI: MI Adjudicated per Universal Definition'**
**'All MI (periprocedural, spontaneous, Q-wave and non Q-wave) including large and small'**
**(And repeatedly emphasised in the protocol)**

**Expert Consensus Document**

**Universal Definition of Myocardial Infarction**

Kristian Thygesen; Joseph S. Alpert; Harvey D. White;
on behalf of the Joint ESC/ACCF/AHA/WHF Task Force
for the Redefinition of Myocardial Infarction

**[CIRC 2007]**

'If troponin assays are not available, the best alternative is CKMB'

**EXCEL PROTOCOL: Definition of Myocardial Infarction [16.1.2.,p 92]**
Different criteria for spontaneous and peri-procedural MI will be utilized.
New biochemical definition (SCAI definition eventually published in JACC 2013)

NEJM 2019: 'Third, a specific bio-marker-based definition of large periprocedural myocardial infarction was used in the present trial; this definition differs from the criteria used in the 3rd UDMI (which was developed while the current trial was ongoing)'. **(But was UDMI (2007) not 3rd UDMI (2012)**

Circulation

[Dec 2018]

WHITE PAPER

# Myocardial Revascularization Trials

## Beyond the Printed Word

**ABSTRACT:** This article reviews the context and evidence of recent myocardial revascularization trials that compared percutaneous coronary intervention with coronary artery bypass grafting for the treatment of left main and multivessel coronary artery disease. We develop the rationale that some of the knowledge synthesis resulting from these trials, particularly with regard to the claimed noninferiority of percutaneous coronary intervention beyond nondiabetic patients with low anatomic complexity, may have been affected by trial design, patient selection based on suitability for percutaneous coronary intervention, and end point

Marc Ruel, MD, MPH
Volkmar Falk, MD, PhD
Michael E. Farkouh, MD, MS
Nick Freemantle, PhD
Mario F. Gaudino, MD
David Glineur, MD, PhD
Duke E. Cameron, MD
David P. Taggart, MD

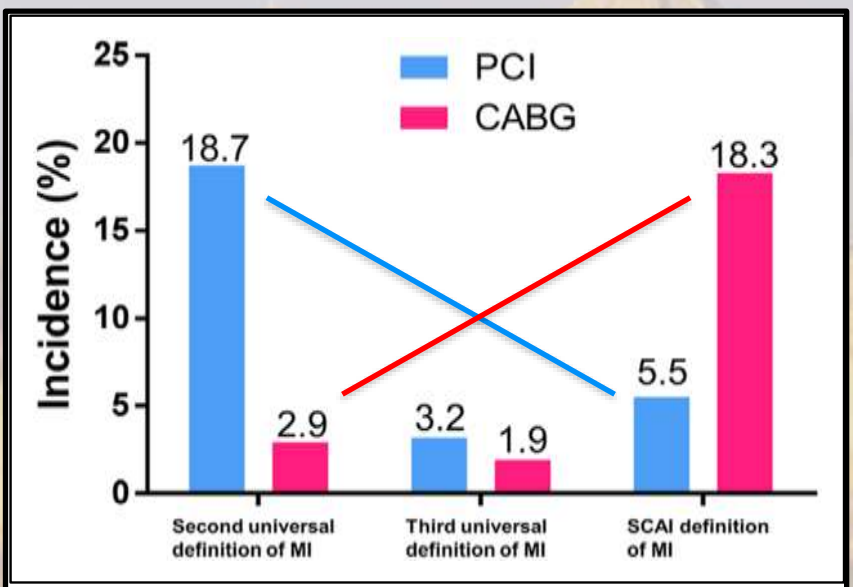



**Figure 1. Rates of periprocedural myocardial infarction (MI) according to various definitions in 7697 patients who received percutaneous coronary intervention (PCI; n=4514) or coronary artery bypass grafting (CABG; n=3183) between 2003 and 2013 and for whom serial measurements of creatine kinase-MB were available.**
SCAI indicates Society for Cardiovascular Angiography and Interventions.
Reproduced from Cho et al[15] with permission. Copyright © 2017, Elsevier.

'Hence a change in the definition of Periprocedural MI, from the original EXCEL trial protocol, contemporary with the 2nd Universal Definition, to the SCAI definition used in the analyses, affected the composite primary end point and the non-inferiority result of the EXCEL study. Without this modification it is plausible that the composite primary end point of MACCE, which included periprocedural MI in the first 30 days, would have changed in favor of CABG.'

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http://dx.doi.org/10.1016/j.jacc.2015.10.036

THE PRESENT AND FUTURE

STATE-OF-THE-ART REVIEW

# Design of Major Randomized Trials

## Part 3 of a 4-Part Series on Statistics for Clinical Trials

Stuart J. Pocock, PhD,* Tim C. Clayton, MSc,* Gregg W. Stone, MD†

**Choice of outcomes**

- Define the primary efficacy endpoint
- Take care in selecting components of composite primary endpoint
- List secondary endpoints
- Incorporate pre-defined safety concerns into overall outcome priorities

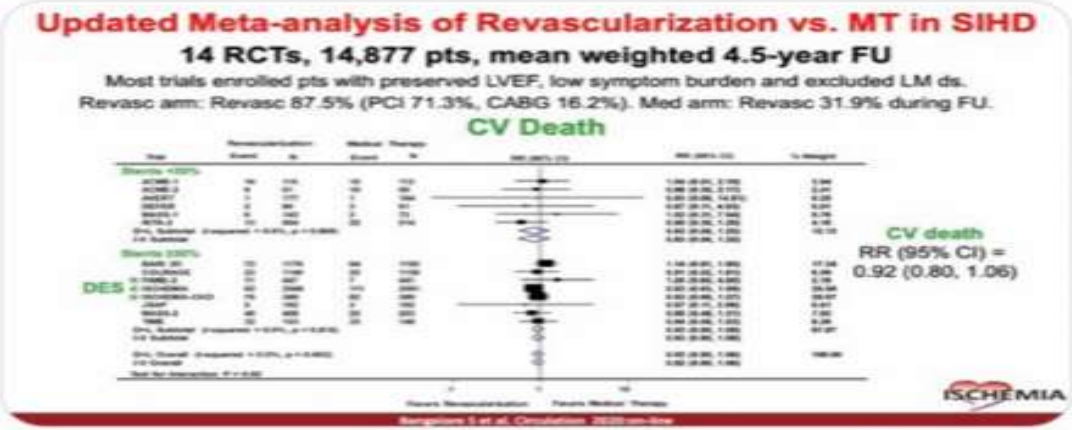
However, what events should contribute to a composite primary endpoint?..... the usual composite is CV death, MI, and stroke. Some are tempted to add in extra components …. this boosts the numbers of events but dilutes the effect and meaning of the composite.. For instance, the most frequent (and often least clinically relevant) component tends to be the driver of event rates (**e.g., enzymatic MIs** or revascularization ….)

BUT THIS IS WHAT HAPPENED IN EXCEL !

# Dr Stone: ISCHAEMIA Trial (vs EXCEL Trial)

**Gregg W. Stone MD** @GreggWS... · 4d

3/3 Non-procedural MIs are more strongly related to CV death than procedural MIs. Thus CV death favored revasc, though NS (RR=0.92, 95% CI 0.80-1.06). Longer-term FU is needed to assess whether reduction in these non-fatal spontaneous events improves long-term survival.

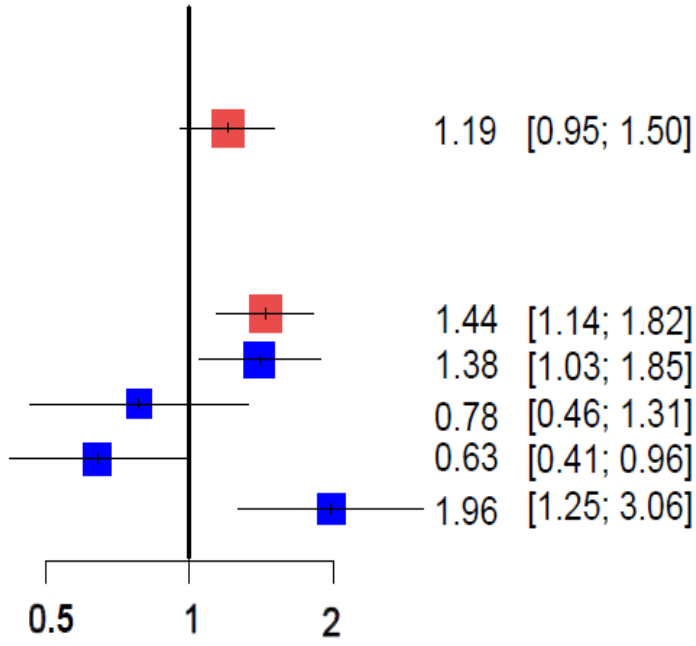



1 10 29

In EXCEL: Primary Outcome defined on procedural MI !!!

# EXCEL EXCLUDING PERI-PROCEDURAL MI (Prof M Gaudino, NY)

| Endpoint | PCI Events | PCI Total | CABG Events | CABG Total | OR | 95%CI |
|---|---|---|---|---|---|---|
| ***Original analysis*** | | | | | | |
| Death, stroke or MI | 203 | 948 | 176 | 957 | 1.19 | [0.95; 1.50] |
| ***Alternate analysis*** | | | | | | |
| Death, stroke, non-peri-procedural MI | 204 | 948 | 153 | 957 | 1.44 | [1.14; 1.82] |
| Death | 119 | 948 | 89 | 957 | 1.38 | [1.03; 1.85] |
| Stroke | 26 | 948 | 33 | 957 | 0.78 | [0.46; 1.31] |
| Peri−procedural MI | 37 | 948 | 57 | 957 | 0.63 | [0.41; 0.96] |
| Non−peri−procedural MI | 59 | 948 | 31 | 957 | 1.96 | [1.25; 3.06] |




CABG a ‘CLEAR WINNER’ for
(i) the Composite End-Point and
(ii) the Individual Components of: Death, Non-Procedural (ie ‘Real’ MI)
(iii) (and Repeat Revascularization)

# CONCERN 4: Failure to Share Data

Data Sharing Statement

## September 28 2019

Stone GW, Kappetein AP, Sabik JF, et al. Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease. N Engl J Med. DOI: 10.1056/NEJMoa1909406.

| Question | Authors' Response |
|---|---|
| Will the data collected for your study be made available to others? | No |
| Would you like to offer context for your decision? | — |
| Which data? | — |
| Additional information about data | — |
| How or where can the data be obtained? | — |
| When will data availability begin? | — |
| When will data availability end? | — |
| Will any supporting documents be available? | — |
| Which supporting documents? | — |
| Additional information about supporting documents | — |
| How or where can supporting documents be obtained? | — |
| When will supporting documents availability begin? | — |
| When will supporting documents availability end? | — |
| To whom will data be available? | — |
| For what type of analysis or purpose? | — |
| By what mechanism? | — |
| Any other restrictions? | — |
| Additional information | — |

This statement was posted on September 28, 2019, at NEJM.org.

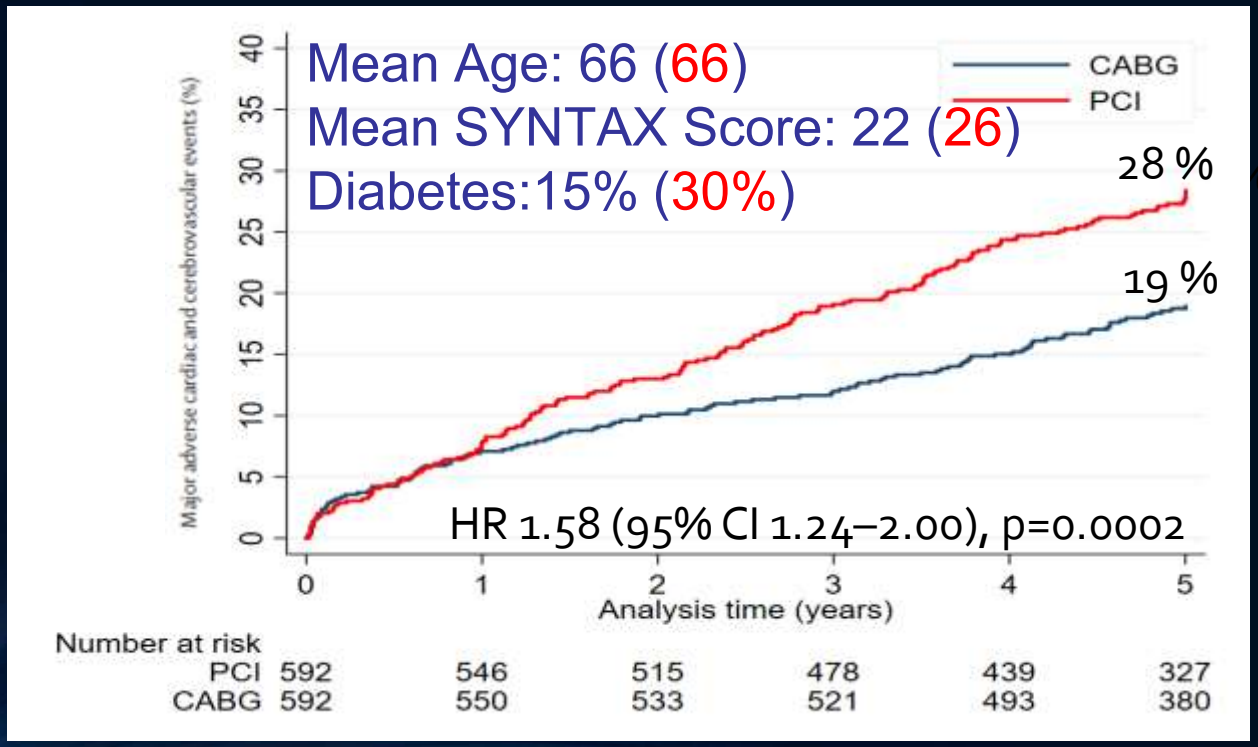
## Why ?

It is conventional to share data

(and several EXCEL authors have published numerous meta-analyses with data from other studies !!)

# Results TCT 2019
# Primary endpoint: MACCE

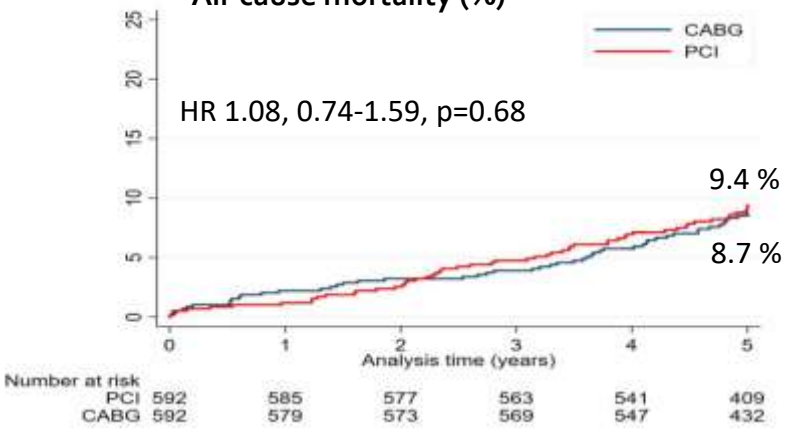
NOBLE vs EXCEL




TCT 2019

evald.christiansen@dadlnet.dk

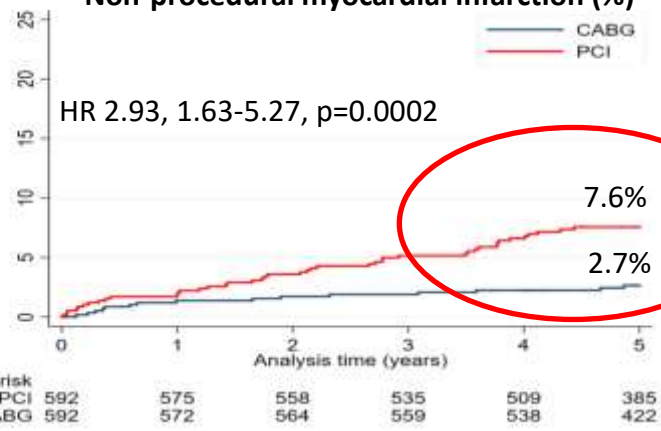
**All-cause mortality (%)**




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| PCI | 592 | 585 | 577 | 563 | 541 | 409 |
| CABG | 592 | 579 | 573 | 569 | 547 | 432 |

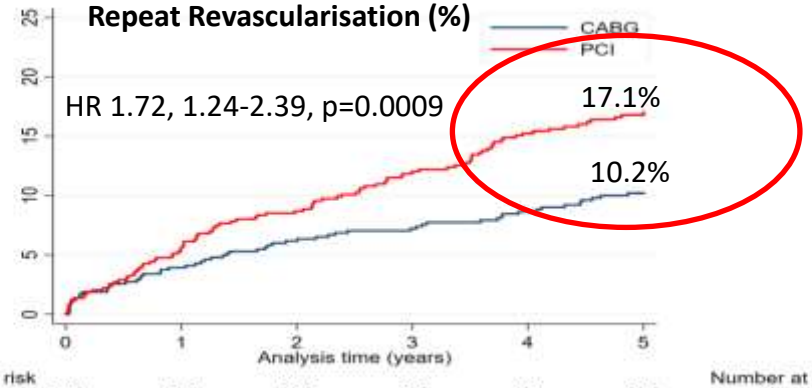
**Non-procedural myocardial infarction (%)**




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| PCI | 592 | 575 | 558 | 535 | 509 | 385 |
| CABG | 592 | 572 | 564 | 559 | 538 | 422 |

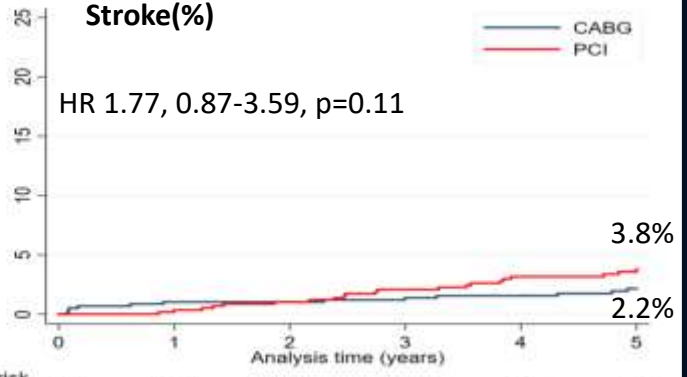
**Repeat Revascularisation (%)**




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| PCI | 592 | 553 | 528 | 499 | 463 | 348 |
| CABG | 592 | 558 | 540 | 530 | 502 | 387 |

**Stroke(%)**




Number at risk

| | | | | | | |
|---|---|---|---|---|---|---|
| PCI | 592 | 583 | 572 | 552 | 525 | 392 |
| CABG | 592 | 573 | 568 | 563 | 540 | 426 |



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NOBLE

# Conclusions:
# NOBLE 5-year follow-up

- The NOBLE trial has reached the predefined number of endpoints and is conclusive
- PCI remained inferior to CABG in 5-year MACCE
- CABG was superior to PCI – also in the group with SYNTAX score <23
- All-cause mortality was similar for PCI and CABG
- PCI resulted in higher rates of non-procedural myocardial infarctions and repeat revascularization



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# EXCEL: The Continuing Debate: What to Believe ?

## Mortality after drug-eluting stents vs. coronary artery bypass grafting for left main coronary artery disease: a meta-analysis of randomized controlled trials

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EHJ 2020
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Interventional
Cardiologists

**Conclusion** The totality of randomized clinical trial evidence demonstrated similar long-term mortality after PCI with DES compared with CABG in patients with LMCAD. Nor were there significant differences in cardiac death, stroke, or MI between PCI and CABG. Unplanned revascularization procedures were less common after CABG compared with PCI. These findings may inform clinical decision-making between cardiologists, surgeons, and patients with LMCAD.

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A record speed?

Meta-analysis 'Magic': Dilute the Largest and Most Definitive trial Of LM (EXCEL) with older, smaller, weaker studies until mortality benefit disappears !

Research

**JAMA Internal Medicine** | Original Investigation

## Bayesian Interpretation of the EXCEL Trial and Other Randomized Clinical Trials of Left Main Coronary Artery Revascularization

James M. Brophy, MD, PhD

JAMA IM 2020
(IF 21)

Non-Interventional
Cardiologist

**CONCLUSIONS AND RELEVANCE** Bayesian analysis assisted in RCT data interpretation and specifically suggested, whether based on EXCEL results alone or on the totality of available evidence, that PCI was associated with inferior long-term results for all events, including mortality, compared with CABG for patients with left main coronary artery disease.

# Summary and Conclusions

**Multi-Vessel Disease (No Left Main):**

**(i) CABG is a Clear Winner for All and Especially in DM**

**Left Main Disease:**

**(i) CABG is a Clear Winner For Those With More Severe Disease (Syntax scores >32)**

**(ii) The two largest and most definitive trials of LM disease in patients with Low/Intermediate Severity Disease (SYNTAX scores < 33) show CABG to be superior to PCI including mortality (in EXCEL) and non-procedural MI and repeat revascularization in both EXCEL and NOBLE.**

Personal View: Current data suggest that there should be a more cautious approach to the use of stents in patients with Low/Intermediate severity Left Main Disease **and especially in younger patients with long life expectancy.**

# 3 REASONS WHY CABG HAS A SURVIVAL BENEFIT OVER PCI

**1** **Anatomically, atheroma is mainly located in the proximal coronary arteries**
Placing bypass grafts to the **MID CORONARY VESSEL** has **TWO** effects
(i) Complexity of proximal '**CULPRIT**' lesion is irrelevant
(ii) Over the long term offers prophylaxis against **FUTURE** proximal 'culprit' lesions
In contrast, PCI only treats **'SUITABLE'** localised proximal 'culprit' lesions but has **NO PROPHYLACTIC BENEFIT** against new proximal disease

**2**

THE NEW ENGLAND JOURNAL OF MEDICINE Aug. 25, 1988

IMA elutes NO into coronary circulation reducing risk of further disease

**DIFFERENCE BETWEEN ENDOTHELIUM-DEPENDENT RELAXATION IN ARTERIAL AND IN VENOUS CORONARY BYPASS GRAFTS**

THOMAS F. LÜSCHER, M.D., DENNIS DIEDERICH, M.D., ROBERT SIEBENMANN, M.D., KURT LEHMANN, M.D.,

**Drug-Eluting Stent and Coronary Thrombosis**
**Biological Mechanisms and Clinical Implications** **[CIRC 2007]**

Thomas F. Lüscher, MD; Jan Steffel, MD; Franz R. Eberli, MD; Michael Joner, MD;

impairs re-endothelialization, downstream endothelial function and creates pro-thrombotic milieu

**3**

PCI means incomplete revascularization (Hannan Circ 2006)
Of 22,000 PCI 69% had incomplete revascularization
>2 vessels (+/- CTO) HR for mortality 1.4 (95% CI = 1.1-1.7)
Residual SYNTAX score >8 increases mortality and MACCE (Farooq, Serruys CIRC 2013)

**PCI will 'never' match the results of CABG for LM/MVD (POBA;BMS;DES)**

# 2018 ESC/EACTS Guidelines on myocardial revascularization

| Recommendations according to extent of CAD | CABG | | PCI | |
|---|---|---|---|---|
| | Class[a] | Level[b] | Class[a] | Level[b] |
| **One-vessel CAD** | | | | |
| Without proximal LAD stenosis. | IIb | C | I | C |
| With proximal LAD stenosis.[68,101,139–144] | I | A | I | A |
| **Two-vessel CAD** | | | | |
| Without proximal LAD stenosis. | IIb | C | I | C |
| With proximal LAD stenosis.[68,70,73] | I | B | I | C |
| **Left main CAD** | | | | |
| Left main disease with low SYNTAX score (0 - 22).[69,121,122,124,145–148] | I | A | I | A |
| Left main disease with intermediate SYNTAX score (23 - 32).[69,121,122,124,145–148] | I | A | IIa | A |
| Left main disease with high SYNTAX score (≥33).[c] [69,121,122,124,146–148] | I | A | III | B |
| **Three-vessel CAD without diabetes mellitus** | | | | |
| Three-vessel disease with low SYNTAX score (0 - 22).[102,105,121,123,124,135,149] | I | A | I | A |
| Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,149] | I | A | III | A |
| **Three-vessel CAD with diabetes mellitus** | | | | |
| Three-vessel disease with low SYNTAX score 0–22.[102,105,121,123,124,135,150–157] | I | A | IIb | A |
| Three-vessel disease with intermediate or high SYNTAX score (>22).[c] [102,105,121,123,124,135,150–157] | I | A | III | A |

66%

79%

CABG would be better if more arterial grafts and greater use of medical therapy !!

# ‘Adjudicated death’ by Clinical Events Committee in EXCEL

| | | PCI % | | CABG% | | |
|---|---|---|---|---|---|---|
| Death from any cause | 119 | 13.0 | 89 | 9.9 | 3.1 (0.2 to 6.1) | 1.38 (1.03 to 1.85) |
| Cardiovascular | 61 | 6.8 | 49 | 5.5 | 1.3 (–0.9 to 3.6) | 1.26 (0.85 to 1.85) |
| Definite cardiovascular | 45 | 5.0 | 40 | 4.5 | 0.5 (–1.4 to 2.5) | 1.13 (0.73 to 1.74) |
| Undetermined cause | 16 | 1.9 | 9 | 1.1 | 0.9 (–0.3 to 2.0) | 1.78 (0.78 to 4.06) |
| Noncardiovascular | 58 | 6.6 | 40 | 4.6 | 2.0 (–0.2 to 4.2) | 1.47 (0.97 to 2.23) |

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**VIEWPOINT**

## Cause of Death in Clinical Research

### Time for a Reassessment?

Michael S. Lauer, MD, FACC,*† Eugene H. Blackstone, MD, FACC,‡ James B. Young, MD, FACC,*† Eric J. Topol, MD, FACC†

*Cleveland, Ohio*

Unreliability of ‘adjudicated’ death in the absence of autopsy

Strongly susceptible to bias (unintended or otherwise)

Patient with cancer can still die of stent thrombosis !!

## Mortality after coronary artery bypass grafting versus percutaneous coronary intervention with stenting for coronary artery disease: a pooled analysis of individual patient data

*Stuart J Head, Milan Milojevic, Joost Daemen, Jung-Min Ahn, Eric Boersma, Evald H Christiansen, Michael J Domanski, Michael E Farkouh, Marcus Flather, Valentin Fuster, Mark A Hlatky, Niels R Holm, Whady A Hueb, Masoor Kamalesh, Young-Hak Kim, Timo Mäkikallio, Friedrich W Mohr, Grigorios Papageorgiou, Seung-Jung Park, Alfredo E Rodriguez, Joseph F Sabik 3rd, Rodney H Stables, Gregg W Stone, Patrick W Serruys, Arie Pieter Kappetein*

**Lancet 2018**
Head et al
N=11,518: FU@ 3.8 yr
**Selected** MVD + LM
SJH, GWS, PWS,APK

## Long-Term Survival Following Multivessel Revascularization in Patients With Diabetes

### The FREEDOM Follow-On Study

Michael E. Farkouh, MD, MSc,[a] Michael Domanski, MD,[b] George D. Dangas, MD, PhD,[c] Lucas C. Godoy, MD,[a,d] Michael J. Mack, MD,[e] Flora S. Siami, MPH,[f] Taye H. Hamza, PhD,[f] Binita Shah, MD, MS,[g] Giulio G. Stefanini, MD,[h] Mandeep S. Sidhu, MD,[i] Jean-François Tanguay, MD,[j] Krishnan Ramanathan, MBChB,[k] Samin K. Sharma, MD,[c] John French, MBChB, PhD,[l] Whady Hueb, MD, PhD,[d] David J. Cohen, MD, MSc,[m] Valentin Fuster, MD, PhD,[c,n] for the FREEDOM Follow-On Study Investigators

**JACC 2018**
Farkouh et al
N = 1,900: FU @ 8 yrs
DM + **Selected** MVD

## Percutaneous coronary intervention versus coronary artery bypass grafting in patients with three-vessel or left main coronary artery disease: 10-year follow-up of the multicentre randomised controlled SYNTAX trial

*Daniel J F M Thuijs, A Pieter Kappetein, Patrick W Serruys, Friedrich-Wilhelm Mohr, Marie-Claude Morice, Michael J Mack, David R Holmes Jr, Nick Curzen, Piroze Davierwala, Thilo Noack, Milan Milojevic, Keith D Dawkins, Bruno R da Costa, Peter Jüni, Stuart J Head, for the SYNTAX Extended Survival Investigators**

**Lancet 2019**
Thuijs et al
N = 1,800: FU@10 yrs
**Selected** MVD + LM
SJH, GWS, PWS,APK

ORIGINAL ARTICLE

## Five-Year Outcomes after PCI or CABG for Left Main Coronary Disease

G.W. Stone, A.P. Kappetein, J.F. Sabik, S.J. Pocock, M.-C. Morice, J. Puskas, D.E. Kandzari, D. Karmpaliotis, W.M. Brown III, N.J. Lembo, A. Banning, B. Merkely, F. Horkay, P.W. Boonstra, A.J. van Boven, I. Ungi, G. Bogáts, S. Mansour, N. Noiseux, M. Sabaté, J. Pomar, M. Hickey, A. Gershlick, P.E. Buszman, A. Bochenek, E. Schampaert, P. Pagé, R. Modolo, J. Gregson, C.A. Simonton, R. Mehran, I. Kosmidou, P. Généreux, A. Crowley, O. Dressler, and P.W. Serruys, for the EXCEL Trial Investigators*

**NEJM 2019**
Stone et al
(*DT withdrew as author)
N = 1,905: FU@5 yrs
**Selected** LM (SS <33)
GWS, PWS,APK

# First NEJM Review of EXCEL (presented on 'BBC Newsnight' Monday 10th Dec 2019)

*(i) The finding of a higher mortality rate in one group than another in a clinical trial (unless the difference is clearly trivial) should receive central emphasis in the report of the results, and we would generally consider it important to include such information in the concluding statement in the final paragraph.*

*(ii) The result of a higher mortality rate in the PCI group, in particular, is addressed in the Discussion in terms that seek to vigorously dismiss the finding as a potential concern. It is emphasized that the differential is mostly accounted for by non-cardiac deaths, although the determination of cause of death is well known to be subject to error and, in an open-label trial, possibly bias.*

2nd version of manuscript accepted by NEJM without these revisions (so I withdrew my authorship)

BBC alleged that
(i) DSMB had raised concerns about excess mortality that was discussed with PI but not the other investigators
(ii) An 80% increase in MI defined by UDMI that was not presented to ESC/EACTS guideline committee
EACTS formally withdrew support for LM guidelines on Monday 10th Dec