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Why don't clinical trial results and guidelines change practice?

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Disclosure

- Nothing to disclose

Some trials do change practice; however, their results are often obvious before they are initiated.

- PCI for STEMI (thrombolysis reduced mortality from MI – Why not PCI?)
- TAVI for inoperable aortic stenosis patients

Reasons trials fail to change practice

- Studying questions when the answer is already known
- Negative or neutral results
- Superiority of unpopular therapies
- Failure of popular therapy to show benefit
- Statistically positive results but without clinical relevance
- Multiple trials of different therapies with no clear answer

Studying questions when the answer is already known

Example: A trial to see if angina is improved
by revascularization

(We know this from clinical observations)

Negative or neutral results

Example: One current generation stent versus another

(industry trials are done to gain labeling, usually with a non-inferiority endpoint)

Superiority of unpopular therapies

Example: Surgery for left main coronary disease and reduced left ventricular function

(Trials led to guideline recommendation for CABG over PCI.)

CLINICAL PRACTICE GUIDELINE: FULL TEXT

2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization

A Report of the American College of Cardiology/American Heart Association
Joint Committee on Clinical Practice Guidelines

Recommendations for Patients With Complex Disease

Referenced studies that support the recommendations are summarized in [Online Data Supplement 13](#).

COR	LOE	RECOMMENDATIONS
1	B-R	1. In patients who require revascularization for significant left main CAD with high-complexity CAD, it is recommended to choose CABG over PCI to improve survival (1,2).
2a	B-R	2. In patients who require revascularization for multivessel CAD with complex or diffuse CAD (e.g., SYNTAX score >33), it is reasonable to choose CABG over PCI to confer a survival advantage (2-5).

Recommendations for Patients With Diabetes

Referenced studies that support the recommendations are summarized in [Online Data Supplement 14](#).

COR	LOE	RECOMMENDATIONS
1	A	1. In patients with diabetes and multivessel CAD with the involvement of the LAD, who are appropriate candidates for CABG, CABG (with a LIMA to the LAD) is recommended in preference to PCI to reduce mortality and repeat revascularizations (1-8).
2a	B-NR	2. In patients with diabetes who have multivessel CAD amenable to PCI and an indication for revascularization and are poor candidates for surgery, PCI can be useful to reduce long-term ischemic outcomes (9,10).
2b	B-R	3. In patients with diabetes who have left main stenosis and low- or intermediate-complexity CAD in the rest of the coronary anatomy, PCI may be considered an alternative to CABG to reduce major adverse cardiovascular outcomes (5,11).

Statistically positive results but without clinical relevance

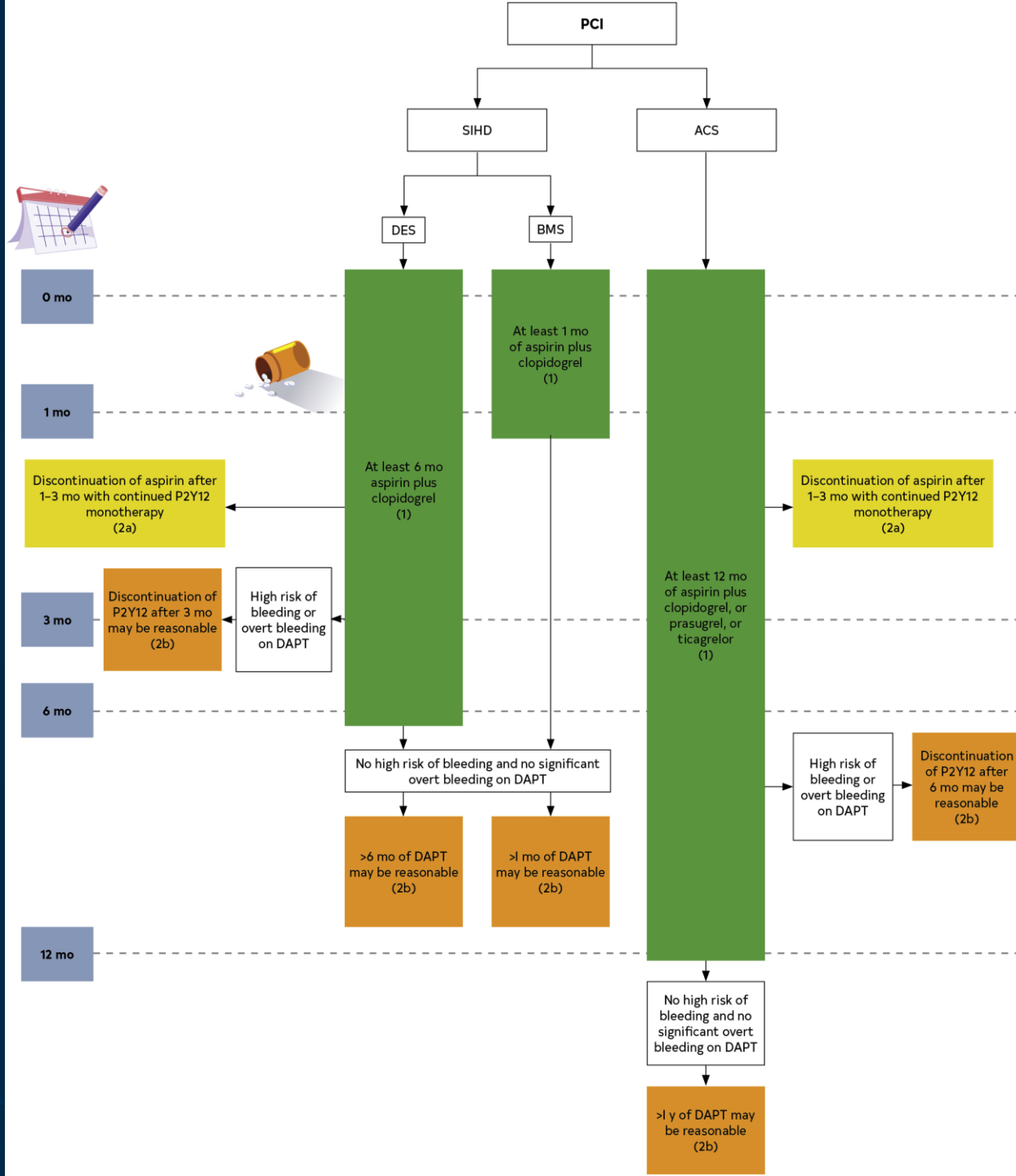
Example: A trial that shows 50% reduction in death or MI but has only an incidence of 2%

(From the patient's perspective, that is a 99% vs 98% chance of not having the adverse outcome.)

Multiple trials of different therapies with no clear answer

Example: Antiplatelet therapy post stent implantation

(DAPT or no DAPT, short duration or longer, platelet testing or genomics)



Failure of popular therapy to show benefit

Example: ISCHEMIA Trial

Circulation

ORIGINAL RESEARCH ARTICLE



Survival After Invasive or Conservative Management of Stable Coronary Disease

Judith S. Hochman¹, MD; Rebecca Anthonopolos, DrPH; Harmony R. Reynolds², MD; Sripal Bangalore³, MD, MHA; Yifan Xu, MPH; Sean M. O'Brien, PhD; Stavroula Mavromichalis, MS; Michelle Chang, MPH; Aira Contreras, MA; Yves Rosenberg, MD, MPH; Ruth Kirby, ASN; Balram Bhargava, MD, DM; Roxy Senior⁴, MD, DM; Ann Banfield, RGN, BSc; Shaun G. Goodman⁵, MD, MSc; Renato D. Lopes⁶, MD, MHS, PhD; Radosław Pracoń⁷, MD, PhD; José López-Sendón⁸, MD; Aldo Pietro Maggioni⁹, MD; Jonathan D. Newman¹⁰, MD, MPH; Jeffrey S. Berger¹¹, MD; Mandeep S. Sidhu, MD; Harvey D. White¹², DSc; Andrea B. Troxel, ScD; Robert A. Harrington¹³, MD; William E. Boden, MD; Gregg W. Stone¹⁴, MD; Daniel B. Mark¹⁵, MD, MPH; John A. Spertus¹⁶, MD, MPH; David J. Maron¹⁷, MD; on behalf of the ISCHEMIA-EXTEND Research Group*

Figure 3

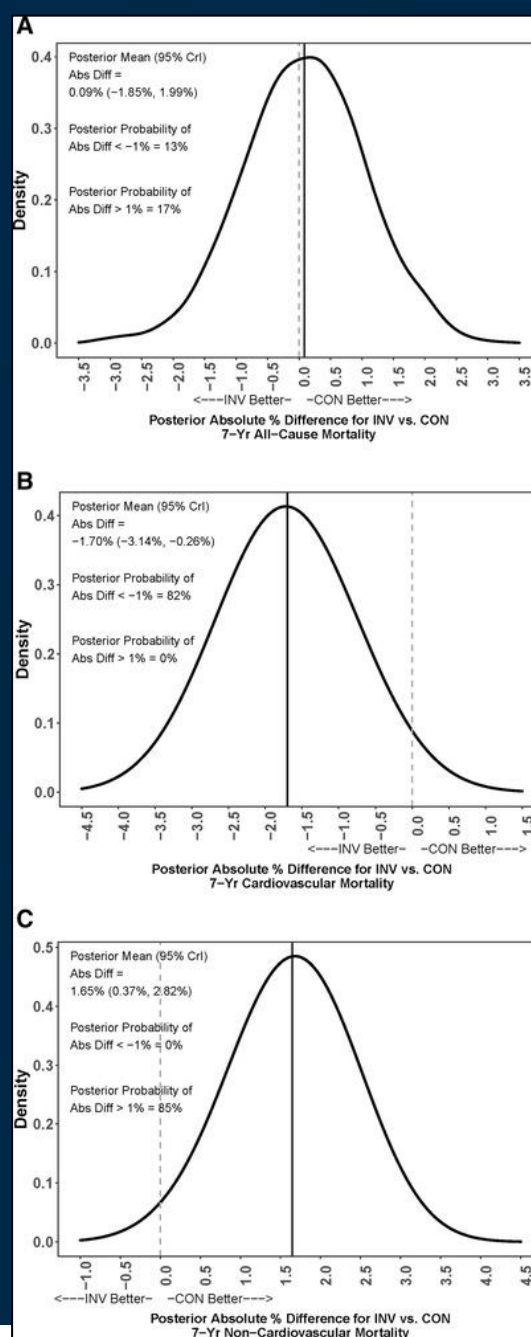


Figure 3 . Probability that one strategy is better than another for 7-year all-cause mortality. Posterior distribution of the adjusted absolute percent difference (Abs Diff) in risk of mortality at 7 years for an invasive (INV) versus conservative (CON) strategy. The gray dashed vertical bar is the null value indicating no difference. The solid black vertical bar is the posterior mean value of the difference. Positive values represent lower mortality for a conservative strategy, and negative values represent lower mortality for an invasive strategy. A, The posterior distribution of the Abs Diff in risk of all-cause mortality at 7 years for an INV versus CON strategy. The solid line is close to the gray dashed null value line, indicating no difference between the groups. B, The posterior distribution of the Abs Diff in risk of cardiovascular mortality at 7 years for an INV versus CON strategy. The concentration of values around -2 indicates a benefit to an invasive rather than conservative strategy by ~2 percentage points. In contrast, in C for noncardiovascular mortality, the posterior distribution of the Abs Diff in risk of noncardiovascular mortality at 7 years for an INV versus CON strategy shows a concentration of values around +2 and indicates a benefit to a conservative rather than invasive strategy by ~2 percentage points.

Trials are, however, necessary to dislodge our incorrect beliefs.

A current trial aimed at establishing that intravascular imaging should be part of PCI is the RENOVATE-COMPLEX-PCI trial.

ORIGINAL ARTICLE

Intravascular Imaging–Guided or Angiography-Guided Complex PCI

J.M. Lee, K.H. Choi, Y.B. Song, J.-Y. Lee, S.-J. Lee, S.Y. Lee, S.M. Kim, K.H. Yun,
J.Y. Cho, C.J. Kim, H.-S. Ahn, C.-W. Nam, H.-J. Yoon, Y.H. Park, W.S. Lee,
J.-O. Jeong, P.S. Song, J.-H. Doh, S.-H. Jo, C.-H. Yoon, M.G. Kang, J.-S. Koh,
K.Y. Lee, Y.-H. Lim, Y.-H. Cho, J.-M. Cho, W.J. Jang, K.-J. Chun, D. Hong,
T.K. Park, J.H. Yang, S.-H. Choi, H.-C. Gwon, and J.-Y. Hahn,
for the RENOVATE-COMPLEX-PCI Investigators*

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NEJM.org.

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As strong as this trial is, in showing that intravascular imaging gives superior results compared with angiography alone, I suspect that practice will be changed by correcting three other things that have inhibited broad use of IVUS:

- lack of experience and training**
- prior history of poor reimbursement**
- poor appreciation of the value of IVUS (operators are familiar with angiographic results but not with IVUS results)**

Will coronary imaging practice be changed because of the RENOVATE-COMPLEX-PCI trial, or because:

- experience and training improves, or
- reimbursement improves, or
- appreciation of the value of IVUS and OCT improves?

The main constraint has been the unfamiliarity with IVUS among operators who have grown up believing the angiogram.

Is my patient like the trial patients?

For patients enrolled in trials, the average outcome is valid; however, trial populations are limited and there is always a bell-shaped curve for benefit, and trial patients are only a sample of patients with the condition.

The question is often, “Is my patient in the middle or at one or the other end of the curve or even outside the distribution of patients studied?”

Registries that contain all the patients of interest constantly show better outcomes with revascularization, but even with adjustment, confounders cannot be eliminated.

However, registries, especially at a local level, more closely resembles our practice experience and feed our opinions.

**Therefore, local
experience often drives
practice more than
clinical trials.**

Conclusions

The results of clinical trials often point toward needed change in practice.

To achieve that change, trials are often **necessary** but seldom **sufficient**.

Trialists should realize this and plan to address unanswered questions with smarter trial design to target appropriate groups, identify clinically relevant endpoints, and imagine **whether the results will ultimately influence practice**.