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The History of Angina and Its Remedies: COURAGE, ORBITA, and A Path Forward

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Abstract

The recent publication of the second Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA-2) trial has renewed debate surrounding the indications and benefits of percutaneous coronary intervention (PCI) in stable angina. ORBITA-2 results show PCI improves anginal symptoms in the absence of antianginal medications. Taken together with the ORBITA-1 and COURAGE trial results, proponents argue that—in contrast to current guidance—PCI and aggressive medical therapy are both equally acceptable initial antianginal strategies, and subject to patient preference. Drawing on the history of randomized studies of interventional management for stable angina, we detail our reservations with this interpretation. More broadly, we highlight the merits of elegantly designed sham-controlled trials in answering lingering clinical questions. Finally, we offer select frameworks for more conclusive trials designed to answer the looming question that cardiologists face: does the landscape of randomized evidence support a medication-first, PCI-first, or shared decision-making treatment paradigm in stable angina?

INTRODUCTION

Angina pectoris is typically the result of spasm or incomplete obstruction of the arteries or microvasculature supplying the myocardium. While multiple variations of angina exist, *stable* angina classically presents with exertional chest discomfort that is relieved with rest or rescue-therapy, commonly sublingual nitroglycerin. Recent estimates suggest that 10 million US adults experience this condition[1] and a portfolio of medical and interventional therapies have arisen to fulfill this burden with price tags per annum on the order of billions of dollars[2].

Some of the earliest descriptions of angina come from the ancient Indian surgeon Sushruta (500 BCE). Sushruta noted the pain to be transient, exertional, precordial, and often afflicting the obese; he advocated for exercise as a preventive measure[3,4]. A millennium later, Leonardo di Vinci helped pioneer our understanding of coronary anatomy; Drs. William Harvey[5] and William Heberden later augmented this coronary map with detailed functional and clinical correlates[6]. In fact, our modern clinical understanding of angina originates with Dr. Heberden's 1772 address to the *Royal College of Physicians*[7]:

> "But there is a disorder of the breast marked with strong and peculiar symptoms, considerable for the kind of danger belonging to it, and not extremely rare, which deserves to be mentioned more at length. The seat of it, and sense of strangling, and anxiety with which it is attended, may make it not improperly be called angina pectoris."

Over a century after Dr. Heberden's address, William Murrell published his landmark *Lancet* paper describing the symptomatic benefit conferred by nitroglycerin among 35 patient case-reports[8]—pioneering the use of vasodilation therapy for treating angina.

SURGERY AS PLACEBO

In investigating the pathogenesis of stable angina, two lines of inquiry emerged: one focused on the role of the coronary arteries as culprits and targets of anti-anginal therapies, and another exploring the role of anastomoses among extra-coronary systems. This work would eventually lead to a series of elegant analyses revealing the effect a placebo intervention could have on anginal pain.

Pre-clinical and histologic work by Mautz throughout the early 20th century observed that non-congenital anastomoses between the coronary system and internal mammary system appear to form following chronic coronary artery occlusion[9]. This led to the theory that bilateral

ligation of the internal mammary artery (BIMAL) could enhance blood flow to the heart via collateral circulation—possibly via retrograde flow from the ligated artery into the coronary system. Shortly after, a number of uncontrolled case-series reporting improvement in angina symptoms[10,11] appeared in the medical literature. Dr. Franklin Miller reports in his historical detailing of the procedure: the apparent success of the operation garnered extensive media attention—with enthusiastic rhetoric like "New Surgery for Ailing Hearts", and reports that a patient's pain had "magically vanished"[12].

Then, in 1959 and 1960, two randomized controlled trials (RCTs) with sham-intervention controls challenged this paradigm. First, in what was one of the earliest sham-controlled studies ever conducted, Cobb et al. randomized 17 patients to either BIMAL or blinded "sham-procedure" consisting of local anesthetic and skin excision without ligating the vessel. At 6-month follow-up, both groups demonstrated improved exercise tolerance, reduced nitroglycerin use, and reported symptomatic improvement. The authors reported, "[Two patients] were able to walk for the full ten minutes of the [endurance] test without angina, whereas before the operation typical angina developed after four or five minutes; both were in the nonligated group."[13] In 1960, Dr. Dimond and colleagues randomized 18 patients to ligation or sham-procedure and found similar results. When asked if they noticed any changes following surgery, one sham-recipient stated "Practically immediately I felt better. I was taking five nitros [nitroglycerin] a day before surgery. In the first five weeks following, I have taken a total of twelve."[14]

These results led Dr. Henry Beecher to publish his landmark "Surgery as Placebo", which provides a quantitative commentary on the findings. Here, referring to the Cobb study specifically, he summarizes the postoperative changes in exercise tolerance, nitroglycerin tablet use, and subjective improvement to show that the placebo effect observed among sham-recipients is quantitatively comparable in size to those measured in other diseases (~35% difference, at the time)[15,16]. Taken together, the results of Cobbs, Dimond, and Beecher's work remind us that interventions intended to improve subjective endpoints may be subject to large placebo effects, necessitating sham-controls in order to discern placebo-from-therapeutic effects.

MEDICATION VERSUS INTERVENTION: TREPIDATIONS AND HARD ENDPOINTS

Since Beecher's essay, management strategies for chronic stable angina have undergone numerous RCTs. These trials have focused on the therapeutic effect of percutaneous coronary intervention (PCI). Most early trials evaluated exercise tolerance and angina relief, comparing two arms—medical therapy versus PCI—without a sham-control, unlike the Cobb and Dimond studies. Combined with insufficient statistical power to detect hard endpoints such as death or MI, these studies failed to convincingly demonstrate benefits of PCI for stable angina.

The ACME Duo

Angioplasty Compared to Medicine (ACME)[17], randomized 212 patients with stable single-vessel coronary artery disease (CAD) to percutaneous transluminal coronary angioplasty (PTCA) or medical therapy. The ACME trial compared these two interventions' impacts on exercise tolerance, angina frequency, and nitroglycerin use at 6-month follow-up. Compared to medical therapy, the PTCA-recipients demonstrated improved total exercise duration (Δ = 96s, $P < .0001$) and time-to-onset of angina symptoms (Δ = 108s, $P < .01$). The PTCA-group also had a 18% greater proportion of individuals reporting resolution of angina symptoms and 26% less participants using oral nitrates ($P<.01$). A follow-up study (ACME-2)[18] later randomized 101 men with two-vessel CAD to PTCA or medical therapy. The purpose of ACME-2 was to assess the subjective and clinical endpoints measured in ACME among a two-vessel disease group in comparison to single-vessel at both 6-month follow-up. Among the two-vessel disease subset at 6-months, exercise time differed by 6s ($P = 0.89$, NS) and time-to-onset of symptoms differed by 18s ($P = 0.58$, NS) between the two intervention groups. Symptom frequency and quality-of-life scores did not differ between the PTCA- and medical therapy groups as well.

The incidence of death and MI were also studied in these trials—with ACME-2 doing so at a 60-month (median) follow-up. Among the single-vessel disease subset, the PTCA group exhibited 5 MIs and 0 deaths, versus 3 MIs and 1 death in the medical therapy group at 6-months. At prolonged follow-up (median 60 months), the PTCA group totaled 14 MIs versus 8 in the medical therapy group, and 15 versus 14 deaths. Among the two-vessel CAD subset, the PTCA group had 2 MIs in the first 6 months (vs. 6 in the medical group), and 6 total at five year follow-up (vs. 6 in the medical group).

Reservations

These trials have been criticized for their lack of statistical power to detect significant effect sizes with respect to hard clinical endpoints. With a reported statistical power of 95% and sample size of 107, we calculate that the trial was powered to detect a ~22% relative difference in the incidence of MI in the single-vessel CAD group. However, the incidence of MI only differed by 1.6% between the two study groups. In order to discern the significance of this effect size, over 3500 people would have needed to be randomized. Similarly, the incidence of MI only differed by ~8% at 6-months among the two-vessel CAD subset. Thus, 380 people would have needed to be randomized to adequately discern this effect size. The authors' explanation for the overall comparable numbers of deaths and MIs between the two treatment groups was that the incidence of incomplete revascularization was higher among those with multi-vessel disease. Additionally, it is plausible that the more epicardial the diseased vessels, the more likely that the angina could be secondary to microvascular disease and thus less likely to be ameliorated by gross revascularization.

With respect to the subjective endpoints, the lack of sham-control limits the interpretations of the ACME trials. As the history of internal mammary artery ligation reminds us, the mere act of receiving the intervention, rather than the intervention itself, can enact a measurable and substantial placebo effect that is inadequately accounted for by a conventional placebo/medical therapy. Taken together, the two ACME trials (1) provided no definitive evidence of reduction in morbidity or mortality; and (2) provided inadequate grounds for discerning the subjective improvements conferred by coronary intervention.

RITA-2

This uncertainty prompted the Coronary Angioplasty versus Medical Therapy for Angina: RITA-2 trial[19]. The largest RCT at its time, RITA-2 randomized over 1000 participants to PTCA or medical therapy. Follow-up ranged from three months to five years. Compared to earlier studies, RITA-2 had a greater number (40%) of participants with two or more diseased coronary arteries. The primary endpoint was combined incidence of death and nonfatal MI, with secondary assessments of exercise tolerance, symptom resolution, and changes in antianginal medication.

In its initial publication (median follow-up of 2.7 years), the investigators found a modest morbidity/mortality *increase* among PTCA-recipients (32 primary events versus 17, P=.02);

though seven of the MIs in the intervention group were attributed to the intervention itself. PTCA-recipients demonstrated an initial symptomatic benefit with 16.5% less incidence of grade II angina (or worse) compared to the medical group at 3-month follow-up. In addition to attenuating to negligible difference by 3-year follow-up, the 95% confidence intervals consistently overlapped throughout the study period with only the 3- and 36-month follow-up rates differing significantly. Regarding exercise duration, the PTCA-recipients showed initial and significant improvements: at 3-months, the difference was ~30s in favor of PTCA. However, this difference attenuated over 6- and 12-month follow-up, ultimately being negligible at 36-months. When stratifying by baseline functional status, PTCA-recipients showed a one-minute increase in exercise duration compared to medical therapy only among the subset of patients with the poorest baseline fitness (≤6 min baseline exercise time); otherwise, times were comparable between groups. Nearly two-thirds of PTCA-recipients were taking at least one antianginal drug after three-year follow-up. In a seven-year follow-up analysis[20], the RITA-2 investigators reported continued attenuation of differences in symptom severity and exercise tolerance. Here, there was a 6.4% difference in grade 2+ angina at five-year follow-up, down from over 10% at one-year follow-up.

Reservations

Regarding subsequent interventions, ~23% of the medical therapy group required follow-up revascularization while 19% of the PTCA group received such. Thus, 25 patients would need to be initially managed with PTCA to avert one subsequent revascularization. Figure 4A and 4C of Henderson et al. (2003) provide further insight: these figures show worsening angina score among both PTCA-recipients and medically-treated participants in the subset of people who would eventually receive non-randomized revascularization. In other words, these are participants whose symptoms were refractory to either (1) initial PTCA, or (2) medical therapy and thus received intervention. In both cases, the novel PTCA confers almost an immediate benefit in angina score, which then plateaus and follows a steadier trend. It is worth asking at this point if such immediate and transient benefit in symptoms is plausible; or if this is evidence of PCI-conferred placebo benefit.

Finally, the rising number of medical-group participants reportedly taking zero antianginals over the three-year follow-up could theoretically be a result of unblinding. After all, recipients of PTCA were treated at randomization and thus antianginal compliance could have

been impacted by simply "having been treated". The medical-therapy group, on the other hand, could be experiencing a sort of "medication fatigue" whereby a perceived lack of treatment could be seeding noncompliance among the participants; perhaps a "reverse placebo effect". Later trials would aim to alleviate these possible compensatory behaviors and placebo effects via double-blinded sham-controls.

COURAGE

In light of the RITA-2 trial, enduring questions regarding the true effect size, circumstances, and timeframe of PCI in conferring a morbidity and mortality benefit remained. Up to this point, prior randomized trials showed mixed evidence of mortality and nonfatal MI reduction among interventionally treated patients. However, cross-sectional studies[21] at the time reported that patients believed that PCI for stable angina was indeed being done to extend life and prevent MI. In light of these enduring questions, the next step was adequately powered trials to assess hard clinical outcomes with these new therapies. The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[22] was the first randomized trial that had sufficient statistical power to assess the effect of optimal medical therapy with or without PCI on combined mortality and nonfatal MI.

COURAGE investigators randomized over 2,200 patients with known, stable coronary artery disease and objective evidence of ischemia to the optimized medical therapy with or without stenting. This medication regimen consisted of anti-ischemic therapies alongside either lisinopril or losartan, and lipid-modifying agents; compliance with a three-drug regimen averaged 90% over three years. Over a median follow-up of 4.6 years, 1,444 lesions were treated with stents with no significant differences in combined death, nonfatal MI, or stroke (HR 1.05 (0.87–1.27), P=0.62). Compared to RITA-2, both groups displayed higher rates of revascularization with 32.6% of the medical-therapy group receiving subsequent revascularization and 21.1% of the PCI-group receiving such (0.60 (0.51–0.71), P<.001). This translates to 11.7 stents needed to be placed to prevent one future revascularization (CABG or PCI). In terms of hard clinical outcomes, COURAGE appeared to settle the score: PCI did not provide any morbidity or mortality benefit over medical therapy. A follow-up report by the COURAGE investigators found reduced angina-symptom frequency and improvements in physical capacity; however, these effects vanished after 36- and 24-months, respectively.

Reservations

In COURAGE, 11.7 stents were required to prevent one future revascularization. Prasad and Cifu[23] note that the cost-effectiveness here is unclear, especially given the lackluster impact on hard clinical outcomes. Such results are consistent with preceding meta-analyses[24]. Additionally, over a longer timescale, a greater number of stents will need to be placed to prevent revascularization. Yet, these findings were met with pushback from stakeholders. As Ioannidis and colleagues[25] measure, counterarguments to COURAGE included perceived insufficient statistical power, results influenced by cross-over, and overly selective inclusion criteria. As the authors note, such critiques of internal and external validity are applicable to almost any randomized trial, no matter how rigorously done.

The COURAGE investigators found strong improvement in quality of life scores at 1-month follow-up among PCI-recipients (P=.001); however, no difference was detected at 6-months. Given the swift strength of this difference and its quick attenuation, a possible and transient placebo-effect may be responsible for these initial reports. One posited explanation[26] for the improvement in symptoms among the medical therapy group is the intensive risk factor control seen over follow-up. Over the five years, the medical therapy group displayed greater reductions in blood pressure and total/LDL cholesterol. Some have argued that this improvement attenuated the relative benefit of PCI over medical therapy via improvements in endothelial function and secondary prevention. However, the differences observed here are small: on the order of 1-2mm Hg or mg/dl. It is unlikely that such differences fail to manifest in death or MI outcomes, but still impact perceived symptomatology. Further, that these differences persist even after the differences between the two groups converge at 36-months further casts doubt on this claim. In fact, whether such small differences are clinically meaningful at all is debatable.

Angina symptoms are highly subject to placebo response from interventional procedures, as the Cobb and Dimond history reminds us. In light of the COURAGE results, Prasad and Cifu, and others, underscored the importance of a sham-controlled randomized study of PCI in angina symptom relief.[12,23]

PERCUTANEOUS CORONARY INTERVENTION AS PLACEBO

ORBITA

In 2018, the Objective Randomised Blinded Investigation with optimal medical Therapy of Angioplasty in stable angina (ORBITA) trial[27] became the first trial since Cobb and Dimond to compare coronary artery revascularization in stable angina to sham therapy. It randomized 200 people with ≥70% single-vessel stenoses to undergo PCI or placebo intervention after a 6-week medication optimization phase. Seventeen patients withdrew due to symptom resolution following medication optimization. Thus, the patients who were randomized were those whose symptoms were refractory to medical management or were patients who actively sought intervention since both groups received such (whether sham or active). Most of the enrolled patients were taking at least two antianginal therapies.

In a sham-controlled trial, maintaining adequate blinding is critical. Here, patients were placed in "auditory isolation" to prevent them from hearing details during the procedure and all support staff (recovery staff; subsequent care providers) were blinded to the patients' treatments. Prior studies had shown that single antianginal drugs could improve exercise time by 48-55 seconds; thus, ORBITA was powered to detect differences on the order of 30 seconds. After 6-week follow-up, the difference in exercise duration between PCI and placebo was 16.6 seconds (95% confidence interval, -8.9 to 42.0 seconds). When re-analyzed using analysis of covariance (ANCOVA), the difference modestly increased to 21.4s (95% confidence interval, -3.4 to 41.1 seconds, P=0.09)[28]. Furthermore, the two groups showed modest improvement in angina symptoms but these improvements, too, were comparable between groups.

Reservations

Recall that Parisi and colleagues[17] initially found upwards of a 96s difference in exercise duration among PTCA-recipients compared to medical therapy. The ORBITA trial tells us that a majority of this benefit was due to the placebo-effect—echoing the legacy of Cobb's and Dimond's findings.

While this sham-controlled study design remains laudable, possible breaches in patient blinding leave lingering gaps for further methodological rigor. Though the investigators took meticulous efforts to conceal group assignment among the patients, biases from the proceduralists themselves could have led to a degree of unblinding. In the ORBITA trial, the sham- and PCI-procedures differed in duration by 30 minutes (P <.0001). This difference could lead to unblinding if the sham-recipients feel that they were given inadequate treatment due to the brevity of the procedure. Methods to separate incomplete sham from therapeutic effect have

been proposed– specifically that a video-recording the procedure be made and employing an outside third-party procedural assessment, which could strengthen the sham-methodology by validating the degree of blinding maintained.[29]

ORBITA-2

Thus far, we have traced the history of interventional versus medical management of stable angina. Initial questions aimed at detecting morbidity and mortality outcomes with off-target benefits detected in angina symptoms and quality-of-life. The COURAGE trial effectively settled the former, shifting the conversation to whether a symptomatic benefit is conferred by PCI. The ORBITA-1 results showed us that PCI provided no additional symptom benefit over aggressive medical therapy. ORBITA-2[30] was designed to answer a different question entirely—the merits of which we will explore.

ORBITA-2 was a 12-week multicenter study of 301 patients randomized to PCI or sham-procedure after a 2-week period of antianginal cessation. The median number of antianginals prescribed prior to cessation was one per patient. Eligibility criteria included radiographic evidence of at least one stenotic coronary vessel (≥50%); and evidence of ischemia. During the 2-weeks of monitoring following medication withdrawal, patients were eligible for randomization only if they reported symptoms during this phase; asymptomatic patients were not randomized. Blinding was maintained in ways similar to the ORBITA-1 trial.

The primary endpoint of ORBITA-2 was a reporting score that is a function of angina symptom severity and antianginals prescribed on a given day. The investigators found that, in the absence of medical therapy, patients receiving sham-procedure were more likely to report daily symptoms (mean odds ratio (OR) = 3.44, 95% CI, 2.00 to 5.91) but comparable antianginal medication use (OR = 1.21, 95% CI, 0.70 to 2.10). PCI-recipients also endured 59s more than sham-recipients on modified Bruce protocol (Δ = 59.5, 95% CI, 16.0 to 103.0).

Reservations

A widely discussed figure from ORBITA-2 is Figure 1A whereby angina symptoms are reported as a function of days-since-randomization. Here, we see a near-immediate benefit among PCI-recipients, with symptom resolution also seen in sham-recipients (though, to a lesser degree). Since PCI is comparable to taking one antianginal medication (as supported by the ORBITA-1 and MARISA[31] trials), this figure could instead be interpreted as comparing the

addition of a single antianginal agent (in lieu of intervention) versus zero (plus some basal improvements secondary to placebo).

Our point here is to highlight that an immediate symptomatic benefit is physiologically plausible among PCI-recipients; however, given its comparable effect size to one antianginal medication, these results are not surprising. Additionally, subgroup analyses from COURAGE revealed that such a difference may vanish after 2-3 years; however, its lack of sham-control limits this interpretation. ORBITA-2 teaches us that novel day-to-day symptom tracking technologies can provide valuable time-to-benefit insights. Repeating older trials with this technology could allow interpreting an intervention's benefit at a higher resolution and add to patient discussions.

Given the landscape of trials preceding it, it is worth asking why the ORBITA-2 investigators withheld antianginals. Investigators contend that withholding the antianginal medications isolates the palliative effect of PCI. Yet, the patients in ORBITA-2 were stabilized on a median of *one* antianginal prior to protocol-mandated cessation of pharmacotherapies—decidedly suboptimal compared to the uptitration goals of ORBITA-1 (2 meds) and certainly those of COURAGE (3 meds). In fact, this reflects the baseline antianginal regimen observed in large European registries.[32] While the ORBITA 2 protocol certainly isolates the effect of PCI alone, it does so in a setting of arbitrarily withholding a non-idealized treatment portfolio. Consequently, ORBITA-2 fails to change clinical guidance in the pragmatic deployment of PCI for stable angina outside settings of total noncompliance or complete medication intolerance.

If, instead, ORBITA 2 allowed patients to continue baseline medications, the trial would have been more pragmatically designed and sham-controlled version of COURAGE—answering the question: for the patient coming in taking their baseline antianginal regimen, what additive benefit does PCI confer?

Implementation Strategies: Missteps, Lingering Questions, and Solution

Should the initial management of stable angina defer to a shared decision-making model whereby PCI and medical management are presented to the patient as reasonable and efficacious first steps? First, we must acknowledge that–ideally–such a framing appeals to both patients and interventionalists alike. For patients, the allure of a one-time fix for a debilitating disease is enormous; especially when weighed against the alternative of continued or increased medication

use. Furthermore, given prior data on the possibility of revascularization despite medical management (due to MI or refractory symptoms), the draw to "get it out of the way" may skew patient decision-making. For the interventionists, both altruistic (and financial) incentives are great as well. While the financial incentives for interventional management are obvious, interventionalists, too, want a more immediate alleviation of their patients suffering. The use of PCI is a sort of "forced compliance" too, whereby the stent is placed and the practitioner does not need to worry as much about the patient's medication compliance or tolerance.

The problem, however, is that neither ORBITA-1 nor ORBITA-2 resolve whether or not such a shared decision-making avenue should be available. In 2020, the International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial[33] aimed to provide some insights into this question. ISCHEMIA randomized over 5,100 patients to early revascularization or aggressive medical therapy (with subsequent revascularization for refractory symptoms) in patients with stress imaging-verified moderate-to-severe ischemia. While the final results of the study showed no difference in death or cardiovascular morbidity between the two strategies, a number of trial-design features limit a clinical translation of the results. First and foremost, all patients underwent blinded coronary CT scans to exclude left main disease. Other limitations include endpoint revision and inadequate blinding via sham-procedure, with possible "faith healing" and "subtraction anxiety" behaviors from both patients and practitioners[34]. Also, neither exercise tolerance nor symptom resolution were studied endpoints.

In light of the ISCHEMIA trial limitations, we are left with incomplete or contradictory indications and implementation strategies for stable angina. Dating back to the ACME trials, repeated statistical underpowering and ethical hesitations regarding sham-procedure have consistently hindered clarity for cardiologists.

Proposals for ongoing studies

The story of PCI in stable angina over the last half century has focused on symptom improvement and quality-of-life. Doctors are now faced with the question of which treatment strategy is most appropriate: stenting first, medications first, or leaving it up to patient choice. Below, we detail trial proposals designed to answer this question.

In one putative trial, patients with stable angina currently managed with medical therapy would be randomized to receive PCI or sham-procedure. By definition, these are patients taking

a varied number of antianginal drugs with refractory symptoms and are thus looking for augmented therapy. These patients should be stratified in at least two ways: first, by the aggressiveness of medical therapy as a function of both milligrams-taken and pill-burden. The nuance here is to distinguish between the strength of a particular medication (e.g 10mg versus 15mg, which may or may not have a burdensome impact on the patient) and the number of pills taken (which may have an impact on the patient's wellbeing). By stratifying patients in this way, we gain a greater sense of the incremental value of PCI. While COURAGE was criticized for its purported unrealistic medication regimen, our study will implicitly separate highly compliant patients (with concomitant confounders, e.g health conscientiousness) from less compliant ones.

Second, patients should be stratified by degree of ischemia as shown on exercise and pharmacologic stress-imaging. In a patient with newly diagnosed stable angina, follow-up testing may reveal varied degrees of myocardial ischemia independent of subjective symptoms.[35] Stratifying patients in this way can provide clarity regarding for what degree of ischemic burden does PCI exert a *subjective* beneficial effect against background medical therapy.

Another trial proposal could assess a shared decision-making (SDM) approach where the choice to initiate PCI or medications to start, with possible revascularization later on. Many variations within this trial design exist and could be subject to follow-up study. Recall from Cobb's and Beecher's[15, 16] work that, in addition to procedures themselves enacting a placebo-effect, such effect is also subject to the enthusiasm (or lack thereof) of the interventionist. Thus, we suggest assessing different data presentation styles and subjective outcomes. Endpoints for such studies could include antianginal burden (in terms of cost, pill number, and tolerability); exercise tolerance (duration and time-to-onset of symptoms); and quality-of-life metrics. The smartphone antianginal-symptom score recording app used in ORBITA-2 would be helpful here. Important for the SDM arm, measuring the degree to which the patient is satisfied with their choice would allow for a more complete interpretation of the objective outcomes measured. For example, imagine a scenario wherein a significant difference is measured in exercise duration in the PCI-choice group (a positive result), but such difference is hardly appreciable or not very significant in the patient's day-to-day reports. This would help sort out any mismatch between significance in trials and for patients. Further analysis of cost would allow for a clearer cost-effectiveness picture per quality-adjusted life year.

Regarding endpoint analyses, per protocol and intention-to-treat (ITT) analyses may be appropriate, though these may be subject to biases in favor of PCI. Our study is intended to discern a pragmatic real-world effect size between initiation strategies; therefore, to account for instances of non-adherence (namely in the conservative-treatment arms), an instrumental variable analysis may be more appropriate.[36]

These potential trial designs have three advantages. First, it would be the first randomized study of initial management strategies for stable angina since ISCHEMIA, with additional parameters to gauge the merits of a SDM model. Additionally, our study incorporates a sham-controlled model similar to the ORBITA studies for improved assessment of subjective endpoints—a limitation of ISCHEMIA and prior studies.

Second, this pragmatic design allows for greater clarity regarding the subjective improvements conferred by PCI versus medical management. While COURAGE was criticized for its arguably unrealistic medication adherence, our design stratifies patients against the background medication therapy they came into the trial on (if already initiated). Thus, any incremental benefit conferred by intervention would be definitionally superior than background therapy and limit any attenuation of interventional effect-size.

Third, our design incorporates cost-effectiveness elements and patient-centered quality-of-life metrics that could reflect a more pragmatic effect of intervention. While the ORBITA studies measured exercise tolerance and symptom frequency, these endpoints are indeed surrogates when taken in isolation. By including cost-effectiveness analyses, investigators could more completely interpret the relative benefit of intervention against other patient-centered values (e.g cost of intervention; the psychological impact of undergoing an invasive procedure).

Conclusions and Remaining Questions

The history of clinical trials assessing treatment strategies for stable angina reminds us that initial trepidations in aggressive trial design can halt progress for decades. Conversely, rigorous trial designs may change the entire conversation within a field. While lingering skeptics remain, the ORBITA trials show us that the field has largely moved beyond the “hard outcomes” questions of the ACME era—a shift largely spearheaded by the COURAGE investigators. Now, the field must grapple with implementation strategies for providing symptomatic relief to angina patients.

While our proposed studies and critiques offer future directions for stable angina management, more questions remain regarding the treatment of this condition. At the time of this writing, no randomized trials exist regarding the optimal dose titration of antianginals or the order in which these drugs should be given. What's more, given the demonstrated placebo-sensitive effect of interventional management for stable angina symptoms, highly rigorous studies challenging intervention against well-studied pharmacotherapy regimens are needed to discern the symptomatic benefit of PCI. While we acknowledge the limitations of applying the findings of ORBITA-2 to clinical practice, thoughtful efforts to parse out the placebo-resistant effects of highly remunerated interventions should continue and deserve praise.

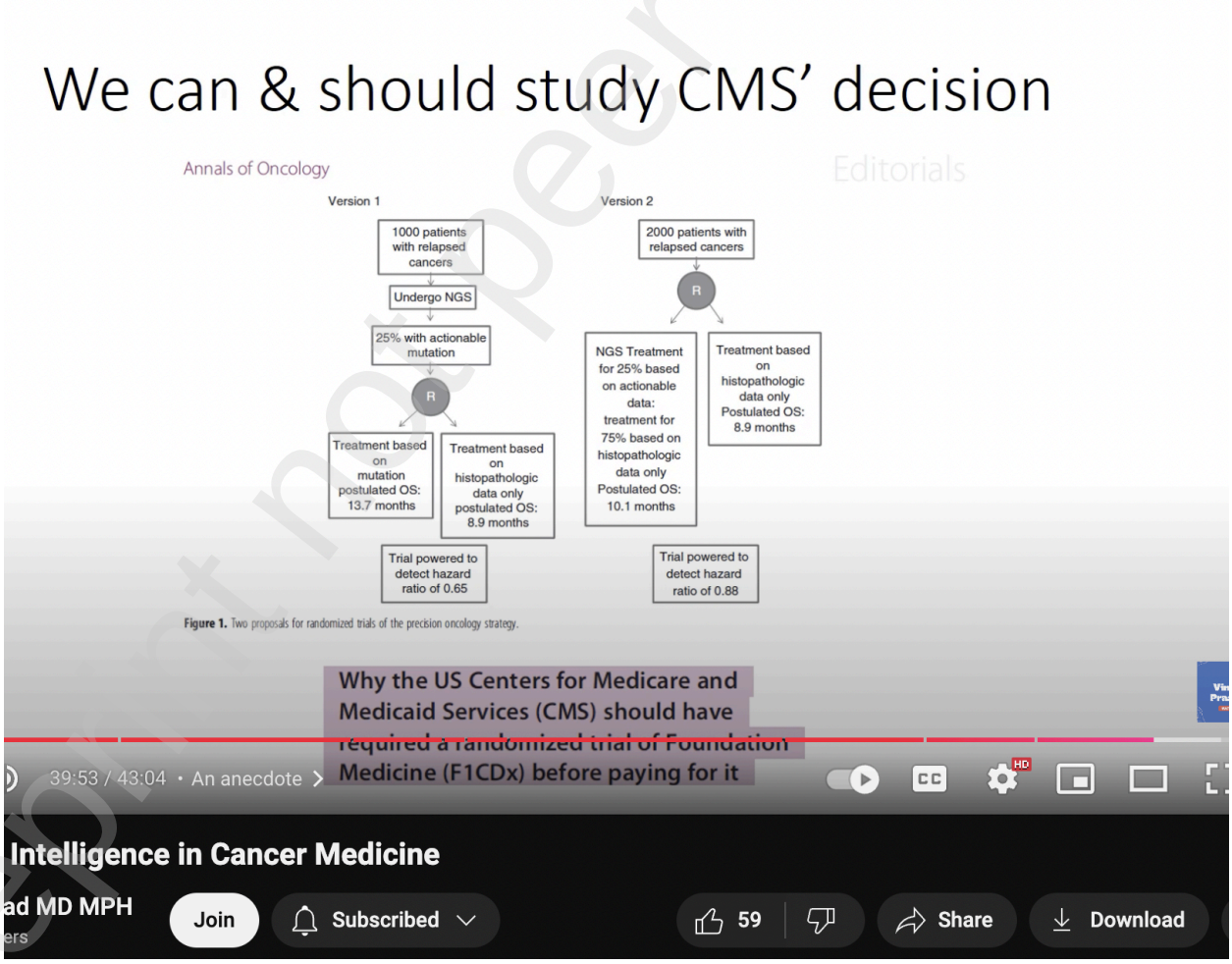

Table 1: Key Trials

Trial	Summary	Limitations
ACME 1992	• Design: 212 patients with EKG-verified positive stress test and 70–99% single-coronary stenosis randomized to PTCA or medical therapy; follow-up: 6 months • Results: PTCA-recipients showed improved exercise duration and symptoms; both groups had comparable incidents of death or MI	• Few clinical events leading to insufficient power to assess death or MI incidence • No sham-blinding for subjective endpoints • Predated use of stents or GP IIb/ IIIa inhibitors • Limited use of secondary CVD prevention
ACME-2 1997	• Design: 101 with two-vessel disease with ACME-stenosis criteria; followed for up to 6 years • Results: no difference time-to-onset of symptoms in single-vessel subgroup b/w treatment arms; in two-vessel, no difference b/w exercise duration, time-to-onset of angina, symptom frequency, or quality of life scores; comparable incidents of death or MI	
RITA-2 1997	• Design: 1018 patients with arteriographically proven stenosis randomized to PTCA or medical therapy; primary endpoint was combined frequency of death and nonfatal MI • Results: At 2.7 year follow-up, primary endpoint occurred 15 more times in PTCA group (P = .02)--seven deaths attributed to procedure. Symptomatically, PTCA-recipients with worse baseline angina/exercise performance showed 1 minuted improvement in exercise duration at 6-months; negligible at two-years	• Climbing rates of participants taking zero antianginals, possibly reflective of unblinding • Lack of sham-control • Immediate, then plateaued, benefit for PTCA-group; possible early evidence of placebo benefit
COURAGE 2007	• Design: 2287 patients on optimized medical therapy ± PCI; median follow-up of 4.6 years; primary outcome was all-cause death and MI • Results: No difference in combined death/MI/stroke; 11.7 stents needed to prevent one future revascularization; transient symptom reduction and exercise improvements among PCI-recipients	• Differences in QoL diminished at 6-months, likely secondary to lack of sham-control • Triple-drug therapy compliance averaged 90%; possibly unreflective of real-world patterns
ORBITA 2018	• Design: 200 patients with ≥70% single-vessel stenoses randomized to PCI or sham-intervention, after 6-week medication optimization period. Primary endpoint: exercise duration • Results: At 6-week follow-up; the two groups differed in exercise duration by 16.6 seconds; 95% confidence interval, -8.9 to 42.0 seconds	• 30 min difference in procedure-duration; possible unblinding
ISCHEMIA 2020	• Design: 5179 patients randomized to early revascularization or medical therapy for initial management. Primary outcomes: composite of death from CV causes, MI, hospitalization from HF; secondary outcomes: angina-related QoL • Results: Initial invasive versus conservative management did not manifest differences in either primary or secondary outcomes	• *Post hoc* revisions of primary endpoint • Lack of sham-control could have influenced revascularization rates among controls • Results sensitive to assessment of ischemia–the definition of which was revised from pre-specified protocol

ORBITA-2 2023	• Design: 301 patients with ≥50% stenosis in ≥1 vessel randomized to PCI or sham-procedure after 2-week antianginal cessation period; primary endpoint: angina-severity score composed of angina symptom frequency and antianginal burden • Results: Sham-recipients were more likely to report daily symptoms; PCI-recipients showed 59s improvement in treadmill testing	• Halted antianginals despite representative compliance • Limited clinical utility regarding initial management strategies

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