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Instrumental Variables with Time-Varying Exposure: New Estimates of Revascularization Effects on Quality of Life

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## ABSTRACT

The ISCHEMIA Trial randomly assigned patients with ischemic heart disease to an invasive treatment strategy centered on revascularization with a control group assigned non-invasive medical therapy. As is common in such "strategy trials," many participants assigned to treatment remained untreated while many assigned to control crossed over into treatment. Intention-to-treat (ITT) analyses of strategy trials preserve randomization-based comparisons, but ITT effects are diluted by non-compliance. Conventional per-protocol analyses that condition on treatment received are likely biased by discarding random assignment. In trials where compliance choices are made shortly after assignment, instrumental variables (IV) methods solve both problems—recovering an undiluted average causal effect of treatment for treated subjects who comply with trial protocol. In ISCHEMIA, however, some controls were revascularized as long as five years after random assignment. This paper extends the IV framework for strategy trials, allowing for such dynamic non-random compliance behavior. IV estimates of long-run revascularization effects on quality of life are markedly larger than previously reported ITT and per-protocol estimates. We also show how to estimate complier characteristics in a dynamic-treatment setting. These estimates reveal increasing selection bias in naive time-varying per-protocol estimates of revascularization effects. Compliers have baseline health similar to that of the study population, while control-group crossovers are far sicker.

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# 1 Introduction

Patients with chronic coronary artery disease may be treated by revascularization, an invasive strategy involving percutenaous coronary intervention (PCI) or coronary artery bypass grafting (CABG). Both are potentially traumatic and resource-intensive interventions. Alternatively, patients may be treated conservatively with a combination of lifestyle changes and drugs. The question of whether the benefits of revascularization for chronic coronary artery disease outweigh the associated risks and costs remains controversial. The recently concluded ISCHEMIA trial assesses the effects of an invasive strategy centered on revascularization on mortality and various measures of quality of life for patients with stable ischemic heart disease and angina. Intention-to-treat (ITT) analyses that compare ISCHEMIA trial participants based on assigned treatment arm show no statistically significant impact on mortality [Spertus et al., 2020*a*,*b*]. ITT estimates of treatment assignment effects on angina frequency and other Seattle Angina Questionaire (SAQ) domain scores suggest invasive treatment produces modest and fading effects on quality of life and angina frequency.

These findings need not be the last word from ISCHEMIA, however, as analyses of ISCHEMIA trial data face important methodological challenges. Problems arise from the fact that the trial saw high rates of treatment group non-adherence (i.e., some assigned to invasive treatment were not revascularized) as well as control group crossovers (i.e., some assigned to conservative treatment were revascularized). Assignment to the invasive treatment group boosted revascularization rates substantially, but not deterministically. Conditional on treatment assigned, patients and their doctors chose whether to receive the revascularization treatment. Such choices, of course, are determined in part by patient frailty and prognosis; they're not independent of potential outcomes.

The timing of control-group crossovers in ISCHEMIA also varied. Some crossovers were revascularized shortly after random assignment, but many waited years for invasive treatment. Consequently, in each follow-up wave, control-group crossovers include a mix of recently-revascularized patients and patients who were revascularized several years ago. This has implications for the estimation of dynamic treatment effects, such as might be seen if revascularization benefits fade.[1]

In the face of self-selection into treatment in a randomized clinical trial, analyses of trial data typically feature intention-to-treat effects and "as-treated" analyses comparing participants who were treated as planned. As we've explained elsewhere [Angrist and Hull, 2023] and review briefly in the next section, ITT effects are diluted by noncompliance with treatment assignment—whether through nonadherence or crossovers. Equally important, per-protocol estimates that group patients by treatment received effectively discard random assignment, opening the door to selection bias. The problem of selection bias can be especially acute for dynamic effects. Among ISCHEMIA participants, control group crossovers are far sicker than the study population. Since the share of crossovers grows over time, as-treated estimates are increasingly biased downwards over time.

[1]The recent British Heart Foundation SENIOR-RITA trial is likewise affected by imperfect compliance and time-varying crossovers [Kunadian et al., 2024]. In this trial, 6% of controls, assigned to conservative treatment, crossed over to angiography within 7 days. As of the five-year follow-up, 24% of controls underwent angiography, and 14% were revascularized. Among patients assigned to invasive treatment, 90% underwent angiography and 50% received revascularization.

This paper addresses these problems by applying the econometric method of instrumental variables (IV). Specifically, we use random assignment to invasive treatment as an instrument for time-varying revascularization exposure, generating new estimates of the quality-of-life gains due to revascularization. On the methodological side, we extend IV methods to capture effects of a time-varying exposure under a set of identifying assumptions well-suited to strategy trials like ISCHEMIA. Our framework yields average causal effects of revascularization exposure on quality of life for patients revascularized as a result of the trial. We also show how to estimate complier characteristics in a dynamic-treatment setting.

The paper is organized as follows. The next section presents the relevant econometric framework, beginning with a review of IV methods applied to clinical trials in a static setting. This is followed by our extension to time-varying exposure and dynamic effects. This section also shows how to identify the characteristics of latent groups defined by a dynamic response to treatment assignment. Section 3 applies the methods of Section 2 to ISCHEMIA. The resulting estimates show substantially larger and more sustained revascularization effects on SAQ summary score and angina frequency scores than ITT or traditional per-protocol analyses would suggest. We also document increasing selection bias in as-treated estimates over time, making these an increasingly misleading guide to revascularization benefits. Section 4 summarizes and briefly discusses implications for other trials.

# 2 Instrumental Variables for Clinical Exposure

## 2.1 Econometric Framework

Our econometric framework is motivated by ISCHEMIA, which randomly assigned trial participants with stable ischemic heart disease to either invasive treatment (angiography as a prelude to intended revascularization) or conservative treatment involving medical therapy alone. Let $Z \in \{0, 1\}$ be a variable indicating invasive assignment. Trial participants' quality of life is measured in each of $\bar{w}$ annual follow-up waves; $Y_w$ denotes quality of life measured in wave $w \in \{1, 2, 3, \ldots, \bar{w}\}$. Treatment is assigned some time in the year ahead of wave 1.[2]

Post-assignment exposure to revascularization is time-varying: many participants assigned conservative were revascularized later, while some assigned invasive were never revascularized or revascularized years after random assignment. Let $T_w \in \{0, 1, 2, \ldots, w\}$ denote *revascularization exposure*, defined as the years a participant has lived since revascularization by wave $w$. In any wave, a trial participant is either never revascularized ($T_w = 0$), revascularized shortly after random assignment ($T_w = w$), revascularized in the year of observation ($T_w = 1$), or revascularized at some other time in between ($1 < T_w < w$).

Potential outcomes capture heterogeneous causal effects of revascularization in each wave.

[2]The trial collected data every few months in the first year and then semi-annually [Spertus et al., 2020*b*]. Our analysis is limited to yearly follow-ups which were generally more extensive. Spertus et al. [2020*b*] uses a Bayesian framework to estimate high-frequency time-varying exposure effects on an ITT basis.

Specifically, let $Y_w(t)$ denote a participant's outcome in wave $w$ when they've lived $T_w = t$ years since revascularization. Once a participant is revascularized, they're revascularized forever. Formally, this means that for all $w \in \{1, ..., \bar{w}-1\}$, $T_w = t$ implies $T_{w+1} = t+1$. This treatment pattern mirrors a staggered adoption setup in differences-in-differences models.[3] Measured in wave $w$, the incremental individual causal effect of revascularization exposure is $Y_w(t) - Y_w(t-1)$. This notation encompasses, for instance, the difference in quality of life that participants experience when revascularized this year versus last year and the difference in quality of life participants experience when revascularized this year versus never. The cumulative effect of revascularization for $t \leq w$ years, observed in wave $w$, is $Y_w(t) - Y_w(0)$. The cumulative effect of revascularization exposure for a participant revascularized shortly after random assignment is therefore $Y_w(w) - Y_w(0)$.

Just as potential outcomes are indexed against treatment received, it's useful to index potential treatment against treatment assigned. To that end, let $T_w(z)$ denote revascularization exposure in wave $w$ when $Z = z$. This is defined for all trial participants, regardless of assignment. The effect of invasive assignment on revascularization exposure in wave $w$ is therefore $T_w(1) - T_w(0)$.

Given an *exclusion restriction*, random assignment makes $Z$ independent of potential outcomes and potential treatments. This *independence assumption* is formalized as:

**Assumption 1** (Independence)**.** *For each wave* $w \in \{1, ..., \bar{w}\}$*, the random variables* $Y_w(0), ..., Y_w(w)$, $T_w(1), T_w(0)$ *are jointly independent of* $Z$*.*

The exclusion restriction in this case asserts that assignment to the invasive arm affects outcomes solely by increasing the likelihood of revascularization.[4] This assumption is plausible in the ISCHEMIA trial, since randomization to the invasive treatment likely had no direct effects on outcomes. Importantly, the exclusion restriction allows assignment to the invasive treatment to affect outcomes via the *timing* of revascularization.

As in Imbens and Angrist [1994] and Angrist and Imbens [1995], we assume that invasive assignment either induces revascularization, makes revascularization happen sooner, or leaves revascularization exposure unchanged. This is formalized as:

**Assumption 2** (Monotonicity)**.** *For each wave* $w \in \{1, ..., \bar{w}\}$*,* $T_w(1) \geq T_w(0)$ *almost surely.*

Given monotonicity, trial participants can be classified in each wave as *compliers* (with $T_w(1) > T_w(0)$), *always-takers* (with $T_w(1) = T_w(0) > 0$), or *never-takers* (with $T_w(1) = T_w(0) = 0$). For always- and never-takers, invasive assignment leaves revascularization exposure unchanged. For compliers, invasive assignment increases exposure.

Invasive assignment is also assumed to generate a *first stage* in wave 1, making the instrument relevant for treatment received shortly after random assignment. That is:

**Assumption 3** (Relevance)**.** $E[T_1 \mid Z = 1] > E[T_1 \mid Z = 0]$.

[3] See, e.g., Athey and Imbens [2022]; Borusyak, Jaravel and Spiess [2024]; Callaway and Sant'Anna [2021]).

[4] Exclusion is formalized by double indexing potential outcomes as in Angrist, Imbens and Rubin [1996]. Let $Y_w(t, z)$ denote a participant's wave-$w$ potential outcome given $t$ years of exposure and assignment $z$. The exclusion restriction says that $Y_w(t, z) = Y_w(t, z')$ for each $t \leq w$, $z$, and $z' \neq z$.

Under Assumption 1, this implies a positive wave-1 first-stage effect on treatment:

$$E[T_1 \mid Z = 1] - E[T_1 \mid Z = 0] = E[T_1(1) - T_1(0)] > 0.$$

Because wave-1 compliers have $T_1(1) > T_1(0)$, the wave-1 first-stage is the probability of wave-1 compliance under Assumption 2. Moreover, because treatment is irreversible, Assumption 3 implies the existence of compliers such that $T_w(1) = w > T_w(0)$ in each wave. In other words, a subset of compliers in each wave experiences the maximum possible $w$ years of revascularization exposure when assigned invasive.

Under Assumptions 1-3, a simple Wald-type IV estimand using wave-1 data identifies the average causal effect of one year of revascularization exposure for wave-1 compliers. Specifically, in wave 1, revascularization exposure, $T_1$, is a Bernoulli treatment that indicates participants revascularized shortly after random assignment. The Imbens and Angrist [1994] local average treatment effect (LATE) theorem applied to wave-1 data therefore implies that:

$$E[Y_1(1) - Y_1(0) \mid T_1(1) > T_1(0)] = \frac{E[Y_1 \mid Z = 1] - E[Y_1 \mid Z = 0]}{E[T_1 \mid Z = 1] - E[T_1 \mid Z = 0]}. \tag{1}$$

The left-hand side of this expression is the average effect of revascularization exposure, $Y_1(1) - Y_1(0)$, on wave-1 compliers. This is obtained by dividing the wave-1 *reduced form* by the wave-1 first stage. The former is defined as the difference in average quality of life between participants assigned invasive and participants assigned conservative, measured in the first wave. The first stage in the Wald denominator is given by the corresponding difference in wave-1 revascularization rates.

In clinical trials, the reduced form is an ITT effect that compares outcomes by treatment assigned, indicated here by $Z$. The share of the trial population for whom treatment status is changed by random assignment is given by the first stage. Equation (1) shows that in a static or short-run analysis of trial data, ITT is diluted relative to the effect of revascularization itself: because the first stage is necessarily between zero and one, the magnitude of LATE exceeds the corresponding ITT effect. Intuitively, because revascularization assignment is assumed to affect outcomes solely by inducing revascularization among compliers, ITT is diluted by averaging in causal effects of zero for always- and never-takers.

IV estimation of per-protocol treatment effects contrast with conventional as-treated analyses of clinical trials that ignore random assignment (see, for instance, the Smith, Coffman and Hudgens [2021] analysis of the CABANA trial comparing treatments for atrial fibrillation). Our as-treated estimates come from ordinary least squares (OLS) regressions of $Y_w$ on $T_w$, with a few baseline controls. Non-random treatment take-up likely biases such estimates; in the LATE framework, this bias can be understood as stemming from differences in health between compliers, always-takers, and never-takers [Angrist, 2004]. We substantiate this view with a comparison of group characteristics in Section 3.3 below.

## 2.2 Identification and Estimation of Dynamic Causal Effects

IV analysis of longer-run effects in the ISCHEMIA trial is complicated by time-varying exposure in a model with heterogeneous potential outcomes. As in Angrist and Imbens [1995] and Rose and Shem-Tov [Forthcoming], the principle complication here arises from the fact that compliance occurs along an extensive margin in which participants who would never have revascularized are induced to revascularize by invasive assignment and an intensive margin in which assignment induces earlier revascularization among participants who would have revascularized anyway. Consequently, complier populations differs for each exposure level and change over time. At the same time, the availability of repeated follow-ups (waves) gives us a handle on this problem that's not been fully exploited in previous applications of IV to models with dynamic effects.

We disentangle dynamic exposure effects with the aid of an assumption that limits effect heterogeneity across waves:

**Assumption 4** (Wave Ignorability)**.** *Average incremental effects for compliers are common across waves: for each pair of waves $w$ and $v \leq w$, and for each exposure time $t \leq v$,*

$$E[Y_w(t) - Y_w(t-1) \mid T_w(1) \geq t > T_w(0)] = E[Y_v(t) - Y_v(t-1) \mid T_v(1) \geq t > T_v(0)] \equiv \lambda_t. \quad (2)$$

Wave ignorability allows incremental exposure effects, $\lambda_t$, to vary freely with exposure time while asserting that incremental effects are independent of the wave in which they're seen. For instance, in a given wave, the incremental effect of revascularization last year $Y_w(1) - Y_w(0)$ may differ from the incremental effect of one year of early exposure, $Y_w(w) - Y_w(w-1)$. Assumption 4 also allows effects to vary for compliers, always-takers, and never-takers. We rule out, however, variation in a given incremental exposure effect across waves. This mirrors restrictions implicit in event study regression models for dynamic causal effects, which typically index causal effects by event time rather than calendar time or treatment cohort (see, e.g., Borusyak, Jaravel and Spiess [2024]).

The following theorem shows that in the LATE framework outlined in the previous section, wave ignorability is sufficient to identify the set of incremental causal effects $\lambda_t$.

**Theorem 1** (Dynamic Incremental Causal Effects)**.** *For each $t \in \{1, ..., \bar{w}\}$, let $D_{wt} = \mathbf{1}[T_w \geq t]$ indicate exposure of at least $t$ periods as of wave $w$. Stack the data across waves and consider a two-stage least squares (2SLS) estimator that uses $Z$ and $Z \times \mathbf{1}[w = t]$ with $t \in \{2, ..., \bar{w}\}$ to instrument the set of $D_{wt}$ in the linear model*

$$Y_w = \mu + \sum_{t=2}^{\bar{w}} \alpha_t \mathbf{1}[w = t] + \sum_{t=1}^{\bar{w}} \lambda_t D_{wt} + \eta_w, \quad (3)$$

*where $\mu$ and $\alpha_t$ are constants and the 2SLS estimand is defined by $E[\eta_w \mid Z] = 0$ for all $w$. Given Assumptions 1-4, coefficients on $D_{wt}$ in this 2SLS estimand equal the vector of $\lambda_t$ defined in (2).*

*Proof.* See Appendix A.2. □

Theorem 1 is proved using the average causal response (ACR) theorem [Angrist and Imbens, 1995].

The ACR theorem shows that the wave-specific IV estimand using $Z$ to instrument $T_w$ with outcome $Y_w$ can be written as a weighted average of incremental complier revascularization effects for each period up to $w$. Under wave ignorability, these incremental effects are common across $w$ and can therefore be obtained by solving a system of linear equations linking wave-specific reduced forms and first stages. The 2SLS estimator described in the theorem implements this solution.

Beyond incremental effects of an additional year of exposure, it's useful to know the average causal effect of each level of exposure relative to a common reference outcome with no exposure—which, for ISCHEMIA, means no revascularization. Conceptually, this cumulates incremental exposure effects. Identification of cumulative revascularization exposure effects can be obtained under a somewhat stronger version of Assumption 4:

**Assumption 5** (Strong Wave Ignorability)**.** *Average incremental effects for compliers at a given level of exposure are common across waves for compliers at any possible margin: for each $t, v, w, v'$, and $t'$ such that $t \leq v \leq w$ and $t \leq t' \leq v' \leq w$,*

$$E[Y_w(t) - Y_w(t-1) \mid T_w(1) \geq t' > T_w(0)] = E[Y_v(t) - Y_v(t-1) \mid T_{v'}(1) \geq t' > T_{v'}(0)] \equiv \lambda_t. \quad (4)$$

Assumption 5 implies Assumption 4 (to see this, set $v' = v$ and $t' = t$ in Assumption 5). In general, however, Assumption 5 adds to Assumption 4 the requirement that a given incremental causal effect be the same at each follow-up wave for complier groups defined over every relevant level of exposure (indexed by $t'$), not just the level at which the incremental effect in question is measured (indexed by $t$). Although stronger than Assumption 4 in the sense of encompassing restrictions on additional latent types, Assumption 5 likewise amounts to the assertion that the point in time at which effects are measured doesn't matter for incremental causal effects at a given level of exposure.

Under strong wave ignorability, average cumulative causal effects are identified and equal to a 2SLS estimand described in the following theorem.

**Theorem 2** (Dynamic Cumulative Causal Effects)**.** *Suppose Assumptions 1-3 and 5 hold. Then:*

*i. For all $w$ and $t \leq w$,*

$$E[Y_w(t) - Y_w(0) \mid T_w(1) \geq t > T_w(0)] = \sum_{i=1}^{t} \lambda_i \equiv \Lambda_t. \quad (5)$$

*ii. For each $t \in \{1, ..., \bar{w}\}$, let $R_{wt} = \mathbf{1}[T_w = t]$. Stack the data across waves and consider a 2SLS estimator that uses $Z$ and $Z \times \mathbf{1}[w = t]$ with $t \in \{2, ..., \bar{w}\}$ to instrument the set of $R_{wt}$ in the linear model*

$$Y_w = \phi + \sum_{t=2}^{\bar{w}} \delta_t \mathbf{1}[w = t] + \sum_{t=1}^{\bar{w}} \Lambda_t R_{wt} + \varepsilon_w, \quad (6)$$

*where $\phi$ and $\delta_t$ are constants and the 2SLS estimand is defined by $E[\varepsilon_w \mid Z] = 0$ for all $w$. The coefficients on $R_{wt}$ in this 2SLS estimand equal the vector of $\Lambda_t$ defined in (5).*

*Proof.* See Appendix A.3. □

The first part of Theorem 2 says that cumulative revascularization effects are identified and equal the sum of incremental revascularization effects. Strong wave ignorability is key to this result: each $\lambda_t$ captures incremental causal effects for different complier groups. A scenario where trial participants have 0-2 years of exposure highlights the role played by Assumption 5 in this context. In this case, the relevant incremental effects at year 2 are $\lambda_1 = E[Y_2(1) - Y_2(0) \mid T_2(1) \geq 1 > T_2(0)]$ and $\lambda_2 = E[Y_2(2) - Y_2(1) \mid T_2(1) \geq 2 > T_2(0)]$, which average over different complier groups. The appendix proof shows that under strong wave ignorability, effects for these groups are the same at a given increment: $E[Y_2(1) - Y_2(0) \mid T_2(1) \geq 1 > T_2(0)] = E[Y_2(1) - Y_2(0) \mid T_2(1) \geq 2 > T_2(0)]$. Hence, $\lambda_1 + \lambda_2 = \Lambda_2$. The second part of Theorem 2 shows that this summing can be automated by instrumenting indicators for the full set of exposure levels $R_{wt}$.

A useful benchmark for dynamic effects arises when incremental causal effects equal zero beyond the first year of revascularization exposure. In this case, revascularization can be seen as a Bernoulli treatment that improves participants quality of life by a fixed and unchanging amount. This scenario justifies a conventional IV estimand that takes a dummy for any exposure as the mediator of causal effects in any wave. In the first wave, this estimand is the same as that for revascularization exposure. The following theorem justifies any-exposure IV for waves $w > 1$.

**Theorem 3** (Any-Exposure IV)**.** *Let $V_w = \mathbf{1}[T_w > 0]$ and suppose Assumptions 1-3 hold. Moreover, for each $w \in \{2, ..., \bar{w}\}$, assume that:*

*i. The instrument is relevant: $E[V_w \mid Z = 1] - E[V_w \mid Z = 0] \neq 0$.*

*ii. Incremental effects are zero beyond one year of exposure:*

$$E[Y_w(t) - Y_w(t-1) \mid T_w(1) \geq t' > T_w(0)] = 0 \tag{7}$$

*for all $t \in \{2, ..., w\}$ and $t' \in \{1, ..., w\}$.*

*Consider the 2SLS estimator that, for a given $w$, uses $Z$ to instrument $V_w$ in*

$$Y_w = \gamma_w + \tau_w V_w + \xi_w, \tag{8}$$

*where $\gamma_w$ and $\tau_w$ are constants and the 2SLS estimand is defined by $E[\xi_w \mid Z] = 0$. Coefficient $\tau_w$ in this 2SLS estimand equals*

$$\tau_w = E[Y_w(T_w(1)) - Y_w(0) \mid T_w(1) \geq 1 > T_w(0)]. \tag{9}$$

*Proof.* See Appendix A.4. □

The causal effects defined in this theorem (the right-hand side of (9)) contrast potential outcomes at any positive exposure with potential outcomes under no exposure. Note that identification of this effect does not require wave ignorability (Assumption 4). Under wave ignorability and the conditions of the theorem, however, $\tau_w$ is constant across waves. Constant $\tau$ can be imposed by stacking specification (8) across waves. Under constant effects, the model is over-identified using

$Z$ and $Z \times \mathbf{1}[w = t]$ with $t \in \{2, ..., \bar{w}\}$ for $V_w$ in the stack. The associated over-identification test statistic is then a test of constant effects.

### 2.3 Characterizing Dynamic Compliers and Always-Takers

In a trial like ISCHEMIA with time-varying exposure, compliance is dynamic: assignment may induce treatment in any wave. An *immediate complier* is treated shortly after random assignment when assigned to be treated, but not otherwise. In later waves, compliance reflects behavior in earlier waves: compliers who would eventually have been revascularized are revascularized sooner when assigned treatment.

We aim to characterize the baseline health of different sorts of compliers, as well as the health of always-takers for whom revascularization timing is unchanged by assignment. In general, treated trial participants are a mix of compliers and always-takers. Complier characteristics are relevant for an assessment of the external validity of IV estimates. In particular, the case for clinical relevance of a set of IV estimates is stronger when the associated compliers have baseline health similar to that of the study population. Moreover, because the treated population includes always-takers, the contrast between complier and always-taker means sheds light on the biases we should expect in as-treated per-protocol estimates.

Identification of latent group characteristics is facilitated by a restriction on compliance timing that we call Immediate Compliers Only (IMCO). In the ISCHEMIA trial, most participants assigned to invasive treatment were revascularized in the first year following assignment, with few induced to revascularize in later years. Turning this empirical observation into an assumption, we have:

**Assumption 6** (IMCO)**.** *Assignment either shifts participants into treatment immediately or has no effect: in each wave* $w \in \{1, ..., \bar{w}\}$, $P[T_w(1) = w \mid T_w(1) > T_w(0)] = 1$.

Assumption 6 says that everyone for whom revascularization exposure is changed by random assignment is revascularized in the first wave.[5] Always-takers, by contrast, are revascularized in the same wave regardless of assignment, though not necessarily the first.

Covariate means for compliers and always-takers in our dynamic setting are identified by the following theorem. Appendix A.1 extends results in the theorem to identify marginal means of potential outcomes.

**Theorem 4** (Dynamic Characterizations)**.** *Let* $X$ *be a baseline covariate, meaning that it's fixed across waves and unchanged by assignment. Suppose that* $(X, T_w(1), T_w(0))$ *is independent of* $Z$ *for all* $w \in \{1, ..., \bar{w}\}$ *and that Assumptions 2-3 hold. Then:*

*i.* Immediate complier means *are given by*

$$E[X \mid T_1(1) > T_1(0)] = \frac{E[\mathbf{1}[T_1 = 1] \times X \mid Z = 1] - E[\mathbf{1}[T_1 = 1] \times X \mid Z = 0]}{E[\mathbf{1}[T_1 = 1] \mid Z = 1] - E[\mathbf{1}[T_1 = 1] \mid Z = 0]}. \tag{10}$$

[5] This can be seen as a flipped version of the Rose and Shem-Tov [Forthcoming] restriction requiring extensive margin compliers only (EMCO). With an ordered treatment under EMCO, everyone whose treatment is increased by assignment moves from $T_w(0) = 0$ to strictly positive $T_w(1)$.

*ii.* Immediate always-taker means *are given by*

$$E[X \mid T_1(1) = T_1(0) = 1] = E[X \mid T_1 = 1, Z = 0]. \tag{11}$$

*Moreover, if Assumption 6 also holds, complier means are constant across waves and equal to immediate complier means:*

$$E[X \mid T_w(1) > T_w(0)] = E[X \mid T_1(1) > T_1(0)] \tag{12}$$

*for all* $w \in \{1, ..., \bar{w}\}$. *Also, given Assumption 6,*

*iii. For each* $w > 1$ *and* $t \in \{0, \ldots, w-1\}$ *such that*

$$E[\mathbf{1}[T_w = t] \mid Z = 1] - E[\mathbf{1}[T_w = t] \mid Z = 0] \neq 0,$$

disaggregated complier means *are given by*

$$E[X \mid T_w(1) = w, T_w(0) = t] = \frac{E[\mathbf{1}[T_w = t] \times X \mid Z = 1] - E[\mathbf{1}[T_w = t] \times X \mid Z = 0]}{E[\mathbf{1}[T_w = t] \mid Z = 1] - E[\mathbf{1}[T_w = t] \mid Z = 0]}. \tag{13}$$

*iv. For each* $w > 1$, later always-taker means *are given by*

$$E[X \mid w > T_w(1) = T_w(0) \geq 1] = E[X \mid w > T_w \geq 1, Z = 1]. \tag{14}$$

Marginal always-takers means, *which average immediate and later always-takers, can be obtained using*

$$\begin{aligned} &E[X \mid T_w(1) = T_w(0) \geq 1] \\ &= \pi_w E[X \mid T_1 = 1, Z = 0] + (1 - \pi_w) E[X \mid w > T_w \geq 1, Z = 1], \end{aligned} \tag{15}$$

*where* $\pi_w = E[\mathbf{1}[T_w = w] \mid Z = 0] / \{E[\mathbf{1}[T_w = w] \mid Z = 0] + E[\mathbf{1}[1 \leq T_w < w] \mid Z = 1]\}$ *is the share of immediate always-takers among all always-takers.*

*Proof.* See Appendix A.5. □

Parts (i) and (ii) of Theorem 4 follow from Imbens and Rubin [1997] and Abadie [2003]: identification of average baseline characteristics for immediate compliers and immediate always-takers is analogous to identification of complier characteristics in a static IV setup. These groups are, respectively, participants revascularized immediately when assigned invasive but not otherwise and participants revascularized immediately regardless of treatment assignment.

The rest of the Theorem 4 uses IMCO (Assumption 6) to identify complier and always-takers means in a dynamic framework. Specifically, equation (13) disaggregates compliers based on the exposure level they attain when assigned conservative. These complier means can be computed using an IV estimand that takes $\mathbf{1}[T_w = t] \times X$ as the outcome while instrumenting $\mathbf{1}[T_w = t]$. Equation (14) recovers average baseline characteristics of those revascularized after the first wave regardless of treatment assignment. Finally, equation (15) combines (11) and (14) to recover the average baseline characteristics of the full set of always-takers as of wave $w$.

# 3 Revascularization Effects on Quality of Life

## 3.1 The ISCHEMIA Trial

The ISCHEMIA trial randomized 5,179 patients with moderate to severe cardiac ischemia to one of two care strategies. Patients assigned to the invasive treatment arm were meant to undergo diagnostic coronary angiography and subsequent revascularization when feasible (through PCI or CABG) while also receiving medical therapy. Conservative-arm patients were meant to receive medical therapy alone, with possible invasive treatment when medical therapy was deemed inadequate [Maron et al., 2020; Spertus et al., 2020*b*].

We analyze trial data from waves 1-5, that is, data collected from one to five years after random assignment. Sample sizes decrease over time since participants who enrolled in the trial later contribute fewer observations ahead of the last follow-up date in December 2018. Roughly 4300 participants contribute to the analysis of quality of life in wave 1, a number that falls to 670 by wave 5. The proportion with followup data is similar by assignment group.[6]

In practice, many ISCHEMIA participants received a treatment different from that assigned. Revascularization rates in the control group, reported in the first column of Table 1, increase from 12% in wave 1 to 29% in wave 5. At the same time, only 80% of those assigned invasive were revascularized initially. Revascularization rates in the group assigned invasive increased from 80% in wave 1 to 83% in wave 5. Importantly, the difference in the likelihood of revascularization by assignment status, reported in the third column of the table, is well below one. Moreover, this gap falls from a high of 68% in the first wave to 54% by wave 5.

Participants assigned to the invasive arm enjoyed a somewhat higher quality of life as a result. ITT effects, reported in columns 5 and 7 of Table 1, show modest treatment-induced gains in SAQ summary scores ranging from 1.6 to just under 3 (these are estimated by differences in raw means, without adjustment for covariates). Angina gains fluctuate around similar magnitudes. Both of these effects can be compared to means of 86-94, with a standard deviations of 13-15. These positive statistically significant ITT effects are a headline finding from the trial. Yet, as explained above, high rates of nonadherence and crossover likely dilute the ITT estimand relative to the effect of revascularization itself.

The theoretical results in the previous section allow us to obtain average causal effects of revascularization exposure measured in years and ranging from 1-5. The assumptions underpinning our IV analysis are that treatment assigned is independent of potential outcomes and potential exposure and that some participants assigned invasive are induced to earlier (or any) exposure as a result with no reversals. The exclusion restriction implicit in Assumption 1 rules out scenarios in which assignment to the invasive strategy improves quality of life with no change in revascularization. It's hard to see a case for random assignment being such a revivifying morale-booster. Assignment to the invasive treatment surely facilitated (rather than inhibited) revascularization for all subjects,

[6]Earlier analyses show mortality is unchanged by treatment assignment, suggesting quality of life comparisons are not biased by differential survival.

ensuring Assumption 2. Subjects assigned to the invasive arm were also much more likely to be revascularized in the first year, a condition sufficient for Assumption 3.

Theorem 3 gives a benchmark for IV analyses of revasculazation exposure: when revascularization matters only to the extent that participants are ever exposed (not how long ago), an any-exposure dummy is the sole mediator of causal effects. Figure 1 plots 2SLS estimates generated by this IV strategy; given restriction (7), these are estimates of $\tau_w$ in Theorem 3. The figure also plots the corresponding ITT esimates (which are the same regardless of how exposure is coded) along with OLS estimates of any-exposure effects. The latter are computed by regressing SAQ outcomes on an any-exposure dummy ($V_w$) in each wave with the same covariates used for IV. In this context, OLS is a conventional as-treated per-protocol analysis strategy that discards random assignment.[7]

2SLS (IV) estimates of any-revascularization effects are larger and more stable over time than ITT effects. For both SAQ outcomes, the latter fall from around four in the first wave to under two in wave 5. This is consistent with the fact that the ITT estimand is diluted by a declining first stage (reported in column 3 of Table 1). 2SLS estimates of SAQ summary score effects, by contrast, are consistently close to four, while 2SLS estimates of angina gains decline from around 5.5 in the initial follow-up year to a fairly stable estimate of three in later waves. OLS estimates of any revascularization effects decline steadily over time, becoming negative by year five. We show below that the increasing divergence between OLS and 2SLS estimates in this figure is a consequence of increasing selection bias in an as-treated analysis.

### 3.2 Dynamic Revascularization Effects

Estimates in Figure 2 suggest that, with one exception, the any-exposure model is not too far off. These estimates of dynamic revascularization exposure effects (relative to no exposure) were computed using equation (6) in Theorem 2. Exposure effects on the SAQ summary score are remarkably stable around four, suggesting revascularization improves quality of life by four points immediately and thereafter. 2SLS estimates suggests revascularization improves angina by 5.5 points initially, with long-run gains constant at around 3 points. Dotted lines in the figure mark the mean of exposure effects for waves 1-5 for summary scores and the mean of exposure effects for waves 2-5 for angina. A test of the hypothesis of equal effects across all waves for summary scores yields a p-value of 0.14. For angina frequency, a test of constant effects across waves 2-5 generates a p-value of 0.86.[8]

2SLS estimates of exposure effects are markedly larger—and statistically distinguishable from—the corresponding OLS estimates. 2SLS estimates, OLS estimates, and the difference between them along with associated standard errors appear in Table 2 for both SAQ outcomes.[9] As can be seen

[7]Estimates in the figure (and tables below) control for baseline angina frequency scores (as in Spertus et al. [2020*b*]) and trial-enrollment region dummies. While not needed for unbiased estimation of revascularization effects under Theorem 3 since the probability of treatment was constant at one-half, these controls boost the statistical precision of estimated effects.

[8]Testing equality of angina score estimates for all five exposure values generates $\chi^2(4) = 36$, a decisive rejection.

[9]Unlike the specification test comparing IV and OLS in Hausman [1978], these standard errors are computed allowing unrestricted correlation between estimators.

in columns 3 and 6 of the table, differences are statistically significant at conventional levels for most of the summary score estimates and for one of the angina score estimates. For both outcomes, joint tests of equality generate decisive rejections. It's also noteworthy that all 2SLS estimates in the table are significantly different from zero while the wave-5 OLS estimates are not.

### 3.3 Contrasting Treated Populations

Comparisons of baseline health measures reveal important differences between participants who do and do not comply with their assigned treatment. Theorem 4 characterizes compliers and always-takers in a dynamic setting by adding IMCO (Assumption 6) to our basic framework.

Histograms of revascularization exposure by assignment, plotted in Figure 3 for each wave, support IMCO: few participants assigned to revascularize were revascularized after wave 1. In wave 2, for instance, participants assigned invasive had either been revascularized for two years and hence immediately after random assignment (i.e., $T_w(1) = 2$) or not at all (i.e., $T_w(1) = 0$). Likewise, in wave 5, participants assigned invasive had either been revascularized for five years or not at all. These patterns are consistent with the presumption that $T_w(1) = w$ for all compliers.

Complier baseline SAQ scores are virtually indistinguishable from those of the overall trial population, while always-takers are substantially sicker. This can be seen by comparing columns 1, 2, and 6 of Table 3, which report baseline scores for the full sample, for immediate compliers, and for always-takers, respectively. The latter quantity is a marginal mean that averages the baseline health of immediate and later always-takers. Means for immediate always-takers, shown in column 5, are similar to the column 6 average; disaggregated complier means and later always-taker means are omitted since—as indicated by Figure 3—few compliers are moved from intermediate levels of exposure to $T_w(1) = w$. The gap between complier and always-taker health is on the order of 10 points; this can be compared with standard deviations of baseline scores of around 19 points when measured in wave 1.

Baseline scores for the population of any-exposure always-takers, moved from no exposure to revascularization in either the first wave or later, are also well below baseline scores for any-exposure compliers. These statistics appear in columns 3 and 8 of Table 3.[10] In contrast with latent groups defined on the basis of years of revascularization exposure, however, the share of any-exposure always-takers among the treated doubles between waves 1 and 5 (as can be seen in column 7 of the table). This reflects the fact that many categorized as any-exposure always-takers (revascularized at some point regardless of assignment) are *exposure* compliers, revascularized immediately instead of later when assigned invasive.

Differences in baseline health between any-exposure compliers and any-exposure always-takers, along with the fact that share treated in the latter category doubles over time, is of substantive importance. This constellation of health differences and changing always-taker shares explain the

[10] For the any-exposure treatment, complier and always-taker means are defined by potential any-exposure dummies $V_w(z) \equiv 1[T_w(z) > 0]$ for $z = 0, 1$. Complier means for participants with $V_w(1) > V_w(0)$ and always-taker means for participants with $V_w(1) = V_w(0)$ are obtained as described for Bernoulli treatments in Angrist and Hull [2023].

decline of OLS (as-treated) estimates in Figure 1. The composition of the treated population defined conventionally, which in our framework equals the population with any exposure, reflects major *compositional* changes. The ever-treated population includes an increasing share of sick patients. Notably, column 4 in Table 3 shows that the share of always-takers among the treated in the exposure analysis is more stable—paralleling relatively stable OLS estimates in Table 2.

Finally, it's noteworthy that compliers' baseline health is reasonably constant over time. Spertus et al. [2020*b*] document differences in quality of life effects for groups with different baseline health. Given this correlation between baseline health and revascularization impact, stable complier health supports wave ignorability, which asserts that incremental exposure effects are constant for compliers revascularized on different dates.

## 4 Summary and Conclusions

This paper develops instrumental variables methods for randomized trials with dynamic treatment exposure and outcomes measured in repeated follow-up waves. Variation in exposure time and repeated follow-ups feature in countless randomized trials. In strategy trials and other pragmatic trials, exposure variation is outside trialists' control once the assignment die has been cast. Initial random assignment notwithstanding, treatment exposure is not randomly assigned.

Dynamic effects in such settings have long posed a challenge for clinical research. Treatment choices made after random assignment are likely correlated with post-trial outcomes. Our dynamic potential outcomes framework identifies average causal effects as a function of exposure time without imposing conditional independence of exposure and potential outcomes or constant effects. Identification here exploits a novel identifying assumption that we've called wave ignorability. As in event-study models, wave ignorability says that exposure effects are unrelated to calendar time. Along with assumptions analogous to those in Angrist and Imbens [1995], wave ignorability delivers identification of incremental and cumulative causal effects of time-varying exposure, both easily computed by 2SLS.

Our framework also enriches the original Angrist, Imbens and Rubin [1996] categorization of treated participants as either compliers or always-takers in two ways. First, we disaggregate complier means into means for trial participants moved into treatment from different points of the untreated exposure distribution. Second, we distinguish means for immediate always-takers who are treated just after random assignment from later always-takers treated regardless of assignment–but not immediately after assignment.

Application of these tools to the ISCHEMIA trial reveal quality of life improvements substantially greater than those that previously-reported ITT and conventional per-protocol estimates would suggest. 2SLS estimates imply revascularization yields sustained gains in SAQ summary scores on the order of four points. ITT analysis, by contrast, generates effects that decline to around two points. For angina, 2SLS yields estimates stable at around three points after an initial bump up to 5.5. For angina too, ITT estimates fall to around two.

No less important, conventional as-treated per-protocol estimates—computed here using OLS regressions on a dummy for any exposure—decline steeply over time. Application of our theoretical results on dynamic latent-group characterization reveal this to be an artifact of the poor health of always-takers. Control group crossovers who are revascularized regardless of assignment are much sicker than compliers. This and the fact that the size of this group grows over time pulls as-treated estimates down to the point where they are negative and not significantly different from zero by wave 5. In sum, conventional per-protocol estimates give an exceptionally misleading view of the payoff to revascularization from a patient's point of view. This offers an interesting contrast to a recent (static) IV analysis of a mammography screening trial. Kowalski [2023] shows mammography always-takers to be healthier than screening compliers, leading conventional per-protocol estimates to exaggerate the gains from screening.

Our analysis of dynamic complier populations stands as weighs against the concern that the IV complier population is likely to be narrow and unrepresentative of any clinical populations of interest (expressed, for instance, in Hernán and Robins [2017]). ISCHEMIA compliers have baseline health much like that of the overall study population. This, of course, is an empirical finding and not a theorem. This finding is not unique to ISCHEMIA, however. In a static IV analysis of colorectal cancer screening trials, Angrist and Hull [2023] show complier characteristics much like those of the population invited for cancer screening. Our work here illuminates a path likely leading to a revision of previously accepted findings in other trials. We've also provided tools to address the question of whether these new estimates are of clinical relevance.

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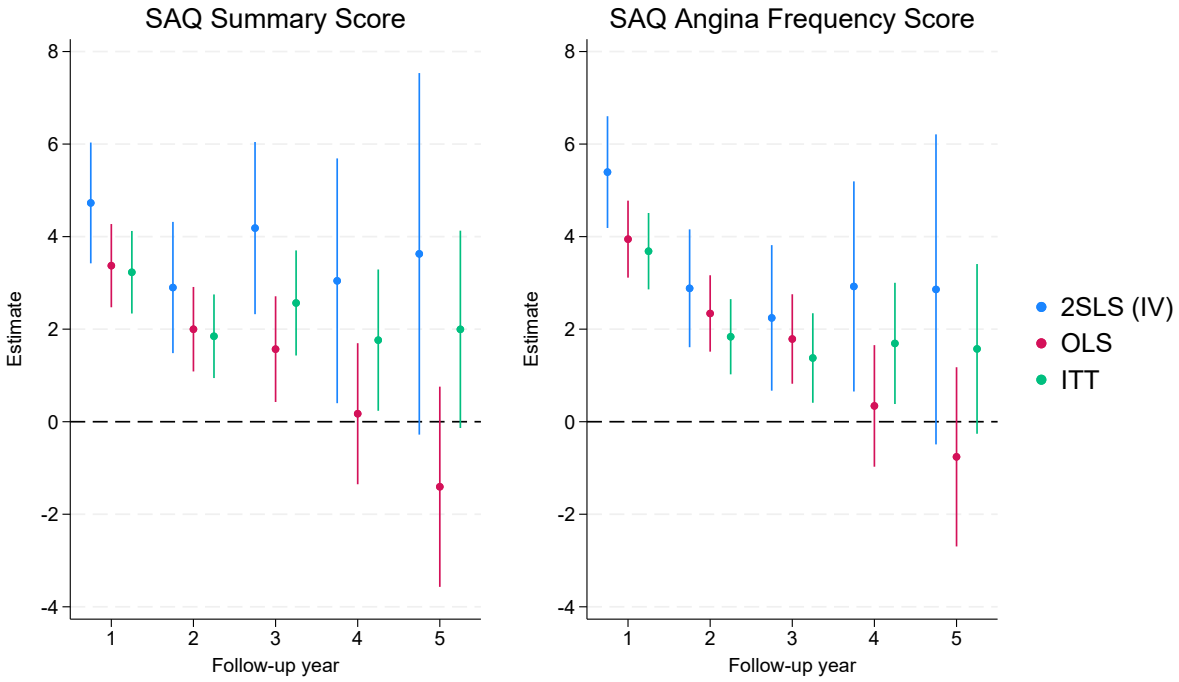
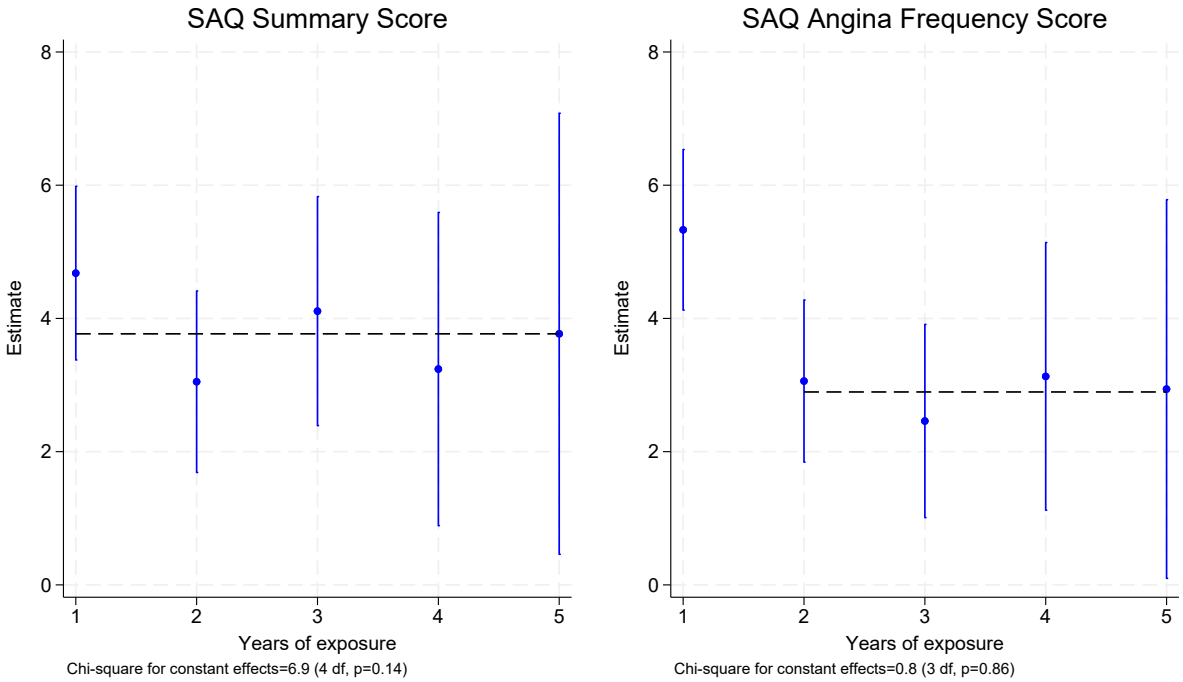
Figure 1: Any-Exposure Revascularization Effects by Wave



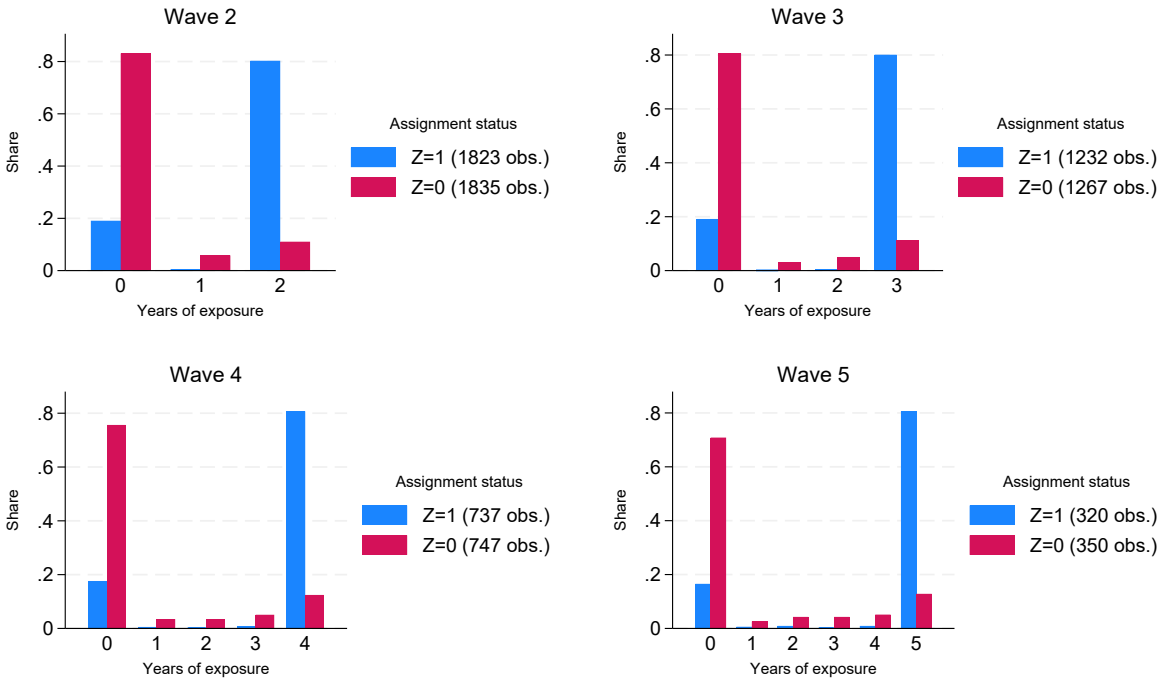

*Notes:* 2SLS (IV) estimates use assignment to instrument any-exposure dummies in each wave (year) following assignment; ITT is the corresponding reduced form. OLS is an as-treated effect. All estimates control for baseline angina frequency scores (as in Spertus et al. [2020*b*]) and enrollment regions.

Figure 2: 2SLS Estimates of Revascularization Exposure Effects




*Notes:* This figure plots 2SLS estimates of average causal effects of 1-5 years of revascularization exposure, relative to never have been revascularized. These estimates control for baseline angina frequency scores (as in Spertus et al. [2020*b*]) and enrollment regions.

Figure 3: Histogram of Revascularization Exposure by Treatment Assigned




*Notes:* This figure plots the histogram of revascularization exposure by follow-up wave. Exposure $T_w = 0$ for participants not revascularized as of wave $w$.

Table 1: Means, Treatment Rates, and ITT Effects

| Follow-up wave | | Revascularization Rate | | Difference in rates | SAQ Summary Score | | SAQ Angina Frequency | |
|---|---|---|---|---|---|---|---|---|
| | | Control Group | Treatment Group | | Mean | ITT | Mean | ITT |
| | | (1) | (2) | (3) | (4) | (5) | (6) | (7) |
| 1 | | 0.117 | 0.802 | 0.686 | 85.7 | 2.96 | 92.1 | 3.42 |
| | | | | (0.011) | [15.7] | (0.474) | [14.6] | (0.440) |
| | N | 2170 | 2146 | | | | | |
| 2 | | 0.169 | 0.809 | 0.640 | 87.3 | 1.61 | 93.3 | 1.56 |
| | | | | (0.013) | [14.6] | (0.481) | [13.2] | (0.434) |
| | N | 1835 | 1822 | | | | | |
| 3 | | 0.194 | 0.809 | 0.615 | 87.4 | 2.34 | 93.7 | 1.22 |
| | | | | (0.016) | [15.1] | (0.604) | [12.9] | (0.515) |
| | N | 1265 | 1230 | | | | | |
| 4 | | 0.244 | 0.823 | 0.579 | 87.7 | 1.65 | 93.9 | 1.62 |
| | | | | (0.021) | [15.4] | (0.798) | [13.3] | (0.688) |
| | N | 747 | 735 | | | | | |
| 5 | | 0.291 | 0.834 | 0.543 | 88.6 | 2.65 | 94.1 | 2.10 |
| | | | | (0.032) | [14.9] | (1.135) | [12.9] | (0.985) |
| | N | 350 | 320 | | | | | |

*Notes:* Column 1 reports the revascularization rate by wave for patients randomized to the conservative treatment group. Column 2 reports the corresponding revascularization rate for those assigned invasive. Column 3 reports the first-stage effect of treatment assignment on revascularization by wave: this is column 2 minus column 1. Columns 4 and 7 report sample means. Columns 5 and 7 report ITT estimates for the effect of treatment assigned. SAQ scores are measured at the time of follow up. Patients who were deceased or did not complete a follow-up questionnaire are omitted. Standard deviations appear in square brackets and standard errors in parentheses.

Table 2: 2SLS and OLS Estimates of Revascularization Exposure Effects

| Years of exposure | SAQ Summary Score | | | SAQ Angina Frequency Score | | |
|---|---|---|---|---|---|---|
| | **2SLS** (1) | **OLS** (2) | **2SLS-OLS** (3) | **2SLS** (4) | **OLS** (5) | **2SLS-OLS** (6) |
| 1 | 4.68 | 1.96 | 2.72 | 5.33 | 2.74 | 2.59 |
| | (0.665) | (0.437) | (0.577) | (0.615) | (0.401) | (0.521) |
| 2 | 3.05 | 1.94 | 1.11 | 3.06 | 2.25 | 0.80 |
| | (0.695) | (0.454) | (0.605) | (0.621) | (0.398) | (0.535) |
| 3 | 4.11 | 1.96 | 2.14 | 2.46 | 2.05 | 0.42 |
| | (0.877) | (0.586) | (0.756) | (0.740) | (0.498) | (0.651) |
| 4 | 3.24 | 2.42 | 0.82 | 3.13 | 2.45 | 0.68 |
| | (1.20) | (0.786) | (1.03) | (1.03) | (0.668) | (0.854) |
| 5 | 3.77 | 1.52 | 2.25 | 2.94 | 1.30 | 1.64 |
| | (1.69) | (1.13) | (1.38) | (1.45) | (0.981) | (1.04) |
| 2SLS-OLS joint test | | 27.99 [0.000] | | | 27.21 [0.000] | |

*Notes:* This table compares 2SLS and OLS estimates of the effects of 1-5 years of revascularization exposure computed using equation (6), stacking data from all waves. Columns 3 and 6 report Hausman [1978]-type t-tests for the difference between 2SLS and OLS estimates, where standard errors are computed using the variance of the difference of estimates. Chi-square statistics at the bottom of the table test 2SLS-OLS joint equality. This statistic has a $\chi^2(5)$ distribution under the null. Estimates were computed with controls for baseline angina frequency scores and enrollment regions. Standard errors, clustered on person, are reported in parentheses. P-values for joint tests appear in brackets in the last row.

Table 3: Complier and Always-Taker Characteristics

| Follow-up wave | Sample mean | Complier means | | Always-takers | | | | |
|---|---|---|---|---|---|---|---|---|
| | | | | Exposure | | | Any-Exposure | |
| | | Exposure | Any-Exposure | Share among treated | Immediate mean | Marginal mean | Share among treated | Mean |
| | (1) | (2) | (3) | (4) | (5) | (6) | (7) | (8) |
| **Panel A: Baseline SAQ Summary Score** | | | | | | | | |
| 1 | 74.3 | 74.5 | 74.5 | 0.26 | 63.6 | 63.6 | 0.26 | 63.6 |
| | [18.9] | (0.589) | (0.589) | | (1.36) | (1.36) | | (1.36) |
| 2 | 74.2 | 73.7 | 73.8 | 0.24 | 64.0 | 64.6 | 0.25 | 67.3 |
| | [18.9] | (0.633) | (0.705) | | (1.51) | (1.46) | | (1.18) |
| 3 | 74.0 | 74.0 | 74.5 | 0.24 | 62.9 | 63.7 | 0.39 | 66.0 |
| | [19.4] | (0.787) | (0.928) | | (1.90) | (1.82) | | (1.43) |
| 4 | 73.8 | 74.4 | 74.7 | 0.27 | 61.3 | 62.3 | 0.46 | 66.8 |
| | [20.1] | (1.08) | (1.37) | | (2.52) | (2.34) | | (1.76) |
| 5 | 74.6 | 75.7 | 77.6 | 0.29 | 65.4 | 67.7 | 0.53 | 67.8 |
| | [20.1] | (1.61) | (2.23) | | (3.68) | (3.15) | | (2.31) |
| **Panel B: Baseline SAQ Angina Frequency Score** | | | | | | | | |
| 1 | 81.5 | 81.2 | 81.2 | 0.26 | 71.8 | 71.8 | 0.26 | 71.8 |
| | [19.5] | (0.630) | (0.630) | | (1.45) | (1.45) | | (1.45) |
| 2 | 81.4 | 80.5 | 80.5 | 0.24 | 71.5 | 72.6 | 0.25 | 75.0 |
| | [19.7] | (0.683) | (0.760) | | (1.63) | (1.56) | | (1.28) |
| 3 | 80.9 | 80.6 | 81.0 | 0.24 | 70.1 | 71.3 | 0.39 | 73.7 |
| | [20.4] | (0.859) | (1.00) | | (2.06) | (1.95) | | (1.51) |
| 4 | 80.6 | 80.7 | 80.7 | 0.27 | 69.3 | 70.9 | 0.46 | 75.0 |
| | [21.0] | (1.17) | (1.47) | | (2.71) | (2.47) | | (1.87) |
| 5 | 81.5 | 83.8 | 85.1 | 0.29 | 71.1 | 73.5 | 0.53 | 75.8 |
| | [20.6] | (1.68) | (2.30) | | (4.00) | (3.35) | | (2.43) |

*Notes:* This table reports complier and always-taker means obtained using Theorem 4 for baseline summary scores (Panel A) and baseline angina frequency scores (Panel B). Column 1 shows overall sample means. Column 2 reports immediate complier means computed using equation (10) for each wave. Column 3 reports any-exposure complier means. The share of always-takers among the treated appears in column 4; this is the denominator of $\pi_w$ divided by sample share of treated. Column 5 reports immediate always-taker means computed using equation (11); column 6 reports marginal always-taker means computed using equation (15). Column 7 reports the share of any-exposure always-takers among the treated and column 8 reports means for this group. Standard deviations appear in square brackets and robust standard errors appear in parentheses.

# A Appendix

## A.1 Marginal Potential Outcome Means

This appendix extends Theorem 4 to identify certain expectations of potential outcomes for different types of compliers and always-takers. Theorem 4 follows from Theorem 5 by setting $Y_w(t) = X$ for all $w$ and all $t$.

**Theorem 5.** *Suppose Assumptions 1-3 hold. Then:*

*i.* Immediate complier means *are given by*

$$E[Y_w(w) \mid T_1(1) > T_1(0)] = \frac{E[\mathbf{1}[T_1 = 1] \times Y_w \mid Z = 1] - E[\mathbf{1}[T_1 = 1] \times Y_w \mid Z = 0]}{E[\mathbf{1}[T_1 = 1] \mid Z = 1] - E[\mathbf{1}[T_1 = 1] \mid Z = 0]}. \tag{16}$$

*ii.* Immediate always-taker means *are given by*

$$E[Y_w(w) \mid T_1(1) = T_1(0) = 1] = E[Y_w \mid T_1 = 1, Z = 0]. \tag{17}$$

*Moreover, if Assumption 6 also holds, then complier means equal immediate complier means in each wave:*

$$E[Y_w(w) \mid T_w(1) > T_w(0)] = E[Y_w(w) \mid T_1(1) > T_1(0)] \tag{18}$$

*for all* $w \in \{1, ..., \bar{w}\}$. *Also, given Assumption 6,*

*iii. For* $w > 1$, *for each* $t \in \{0, \ldots, w-1\}$ *such that* $E[\mathbf{1}[T_w = t] \mid Z = 1] - E[\mathbf{1}[T_w = t] \mid Z = 0] \neq 0$, disaggregated complier means *are given by*

$$E[Y_w(t) \mid T_w(1) = w, T_w(0) = t] = \frac{E[\mathbf{1}[T_w = t] \times Y_w \mid Z = 1] - E[\mathbf{1}[T_w = t] \times Y_w \mid Z = 0]}{E[\mathbf{1}[T_w = t] \mid Z = 1] - E[\mathbf{1}[T_w = t] \mid Z = 0]}. \tag{19}$$

*iv. For* $w > 1$, later always-taker means *are given by*

$$E[Y_w(T_w(1)) \mid w > T_w(1) = T_w(0) \geq 1] = E[Y_w \mid w > T_w \geq 1, Z = 1]. \tag{20}$$

Marginal always-takers means*, which average immediate and later always-takers, can be obtained using*

$$\begin{aligned} &E[Y_w(T_w(1)) \mid T_w(1) = T_w(0) \geq 1] \\ &= \pi_w E[Y_w \mid T_w = w, Z = 0] + (1 - \pi_w) E[Y_w \mid w > T_w \geq 1, Z = 1], \end{aligned} \tag{21}$$

*where* $\pi_w = \frac{E[\mathbf{1}[T_w = w] \mid Z = 0]}{E[\mathbf{1}[T_w = w] \mid Z = 0] + E[\mathbf{1}[1 \leq T_w < w] \mid Z = 1]}$.

*v. Finally, for each each* $t \in \{0, \ldots, w-1\}$, disaggregated always- and never-taker means *are given by*

$$E[Y_w(t) \mid T_w(1) = T_w(0) = t] = E[Y_w \mid T_w = t, Z = 1]. \tag{22}$$

*For never-takers, set $t = 0$. This last result does not require IMCO (Assumption 6).*

*Proof.* See Appendix A.5. □

## A.2 Proof of Theorem 1

As in the proof to Theorem 1 in Angrist and Imbens [1995], Assumptions 1-2 can be used to show that the reduced form for wave-specific IV with outcome $Y_w$ and $T_w$ instrumented by $Z$ for each $w \in \{1, ..., \bar{w}\}$ can be written:

$$\rho_w = \sum_{t=1}^{w} E[Y_w(t) - Y_w(t-1) | T_w(1) \geq t > T_w(0)] \pi_{wt},$$

where $\pi_{wt} \equiv P[T_w(1) \geq t > T_w(0)]$. Under Assumption 4, this becomes:

$$\rho_w = \sum_{t=1}^{w} \lambda_t \pi_{wt}.$$

Let $\rho$ denote the vector of $\rho_w$, with $\Pi$ being a lower-triangular matrix with non-zero elements $\pi_{wt}$ ($w$-th row, $t$-th column). Finally, let $\lambda$ be the vector of $\lambda_t$. Then, we can write:

$$\rho = \Pi\lambda.$$

Under Assumption 3 (wave ignorability), $\Pi$ is invertible since it is lower-triangular with non-zero diagonal elements (absorbing treatment implies $\pi_{ww} = \pi_{11}$ for all $w$). Hence:

$$\lambda = \Pi^{-1}\rho. \tag{23}$$

The 2SLS procedure described in the theorem using equation (3) has reduced form and first stage parameter vectors identical to the stacked wave-by-wave reduced form and first stage described here since the stacked model interacts $Z$ with wave dummies and allows wave-specific intercepts. Hence, these parameters satisfy (23).

## A.3 Proof of Theorem 2

We first show that $\sum_{i=1}^{t} \lambda_i = E[Y_w(t) - Y_w(0) \mid T_w(1) \geq t > T_w(0)]$ under Assumption 5 (strong wave ignorability), for any $w$ and $t \leq w$. Note that for all $i < t$:

$$\{T_i(1) \geq i > T_i(0)\} \iff \{T_t(1) \geq t > T_t(0)\},$$

since, with an absorbing treatment, those with $t$ months exposure at wave $t$ must have been exposed initially. Immediate compliers on the right therefore have $i$ months exposure at every wave $i$ before

wave $t$. Hence, for any $i < t$:

$$E[Y_i(i) - Y_i(i-1)|T_i(1) \geq i > T_i(0)] = E[Y_i(i) - Y_i(i-1)|T_t(1) \geq t > T_t(0)].$$

Moreover, for any $i < t$, strong wave ignorability implies:

$$E[Y_i(i) - Y_i(i-1)|T_i(1) \geq i > T_i(0)] = E[Y_w(i) - Y_w(i-1)|T_w(1) \geq i > T_w(0)].$$

and

$$E[Y_i(i) - Y_i(i-1)|T_t(1) \geq t > T_t(0)] = E[Y_w(i) - Y_w(i-1)|T_w(1) \geq t > T_w(0)].$$

Thus:

$$\begin{aligned}
\sum_{i=1}^{t} \lambda_i &= \sum_{i=1}^{t} E[Y_w(i) - Y_w(i-1)|T_w(1) \geq i > T_w(0)] \\
&= \sum_{i=1}^{t} E[Y_w(i) - Y_w(i-1)|T_w(1) \geq t > T_w(0)] \\
&= E\left[\sum_{i=1}^{t} Y_w(i) - Y_w(i-1) \middle| T_w(1) \geq t > T_w(0)\right] \\
&= E[Y_w(t) - Y_w(0) \mid T_w(1) \geq t > T_w(0)].
\end{aligned}$$

Next, note that $R_{wt} = \sum_{i=1}^{t} D_{wi}$. It follows that the 2SLS estimand instrumenting $R_{wt}$ in equation (6) generates the sum of coefficients from the 2SLS estimand instrumenting $D_{wt}$ in equation (3). That is, $\sum_{i=1}^{t} \lambda_i = \Lambda_t$.

### A.4 Proof of Theorem 3

Fix $w \in \{2, ..., \bar{w}\}$. As in the proof of Theorem 1, Assumptions 1-2 imply that the the reduced form of wave-specific IV regression of $Y_w$ on $V_w$ instrumented by $Z$ can be written as:

$$\rho_w = \sum_{t=1}^{w} E[Y_w(t) - Y_w(t-1)|T_w(1) \geq t > T_w(0)]\pi_{wt},$$

for $\pi_{wt} \equiv P[T_w(1) \geq t > T_w(0)]$. The restriction on incremental effects in the statement of the theorem implies

$$\rho_w = E[Y_w(1) - Y_w(0) \mid T_w(1) \geq 1 > T_w(0)]\pi_{w1}.$$

Note that $\pi_{w1} = P[T_w(1) \geq 1 > T_w(0)] = E[\mathbf{1}[T_w(1) > 0] - \mathbf{1}[T_w(0) > 0]] = E[V_w \mid Z = 1] - E[V_w \mid Z = 0]$. This shows that $\tau_w = E[Y_w(1) - Y_w(0) \mid T_w(1) \geq 1 > T_w(0)]$.

Now, for any $v \in \{2, ..., w\}$,

$$E[Y_w(v) - Y_w(0) \mid T_w(1) \geq 1 > T_w(0)] = \sum_{t=1}^{v} E[Y_w(t) - Y_w(t-1) \mid T_w(1) \geq 1 > T_w(0)]$$
$$= E[Y_w(1) - Y_w(0) \mid T_w(1) \geq 1 > T_w(0)],$$

where the second equality follows from setting $t' = 1$ in the condition on incremental effects on the statement of the theorem. Therefore, $\tau_w = E[Y_w(v) - Y_w(0) \mid T_w(1) \geq 1 > T_w(0)]$ for any $v \in \{1, ..., w\}$, which concludes the proof.

### A.5 Proof of Theorems 4 and 5

Theorem 5 in Appendix A.1 generalizes Theorem 4 to identify expectations of potential outcomes as well as covariate means for compliers and always-takers with dynamic exposure. Proof of Theorem 5 therefore establishes Theorem 4.

Consider the first two results, (16) and (17), which do not require Assumption 6. Fix $w \in \{1, ..., \bar{w}\}$. Because treatment is irreversible, $T_w = w$ if, and only if, $T_1 = 1$. Monotonicity then implies:

$$\begin{aligned} E[\mathbf{1}[T_1 = 1] \times Y_w \mid Z = 1] =& E[\mathbf{1}[T_1(1) = 1] \times Y_w(w)] \\ =& P[T_1(1) = T_1(0) = 1] E[Y_w(w) \mid T_1(1) = T_1(0) = 1] \\ &+ P[T_1(1) > T_1(0)] E[Y_w(w) \mid T_1(1) > T_1(0)]. \end{aligned}$$

Analogously, $E[\mathbf{1}[T_1 = 1] \times Y_w \mid Z = 0] = P[T_1(1) = T_1(0) = 1] E[Y_w(w) \mid T_1(1) = T_1(0) = 1]$, which establishes equation (16). Equation (17) follows from $E[Y_w \mid T_1 = 1, Z = 0] = E[Y_w(w) \mid T_1(0) = 1] = E[Y_w(w) \mid T_1(1) = T_1(0) = 1]$ under monotonicity.

Now, for a given $w \in \{2, ..., \bar{w}\}$, consider results in the theorem that depend on Assumption 6:

1. To establish (18), note that because treatment is irreversible, $T_1(1) > T_1(0)$ implies $T_w(1) > T_w(0)$. Conversely, $T_w(1) > T_w(0)$ implies $T_w(1) = w$ almost surely, which in turn implies $T_1(1) > T_1(0)$ because treatment is irreversible.

2. Fix $t \in \{0, ..., w-1\}$. Note that when $Z = 1$, $\mathbf{1}[T_w = t] = 1$ if and only if $T_w(1) = t$. Therefore, under Assumptions 2 and 6, $E[\mathbf{1}[T_w = t] \mid Z = 1] = P[T_w(1) = T_w(0) = t \mid Z = 1]$ since compliers have $T_w(1) = w$ almost surely. Moreover, under monotonicity,

$$E[\mathbf{1}[T_w = t] \times Y_w \mid Z = 1] = P[T_w(1) = T_w(0) = t] E[Y_w(t) \mid T_w(1) = T_w(0) = t]. \quad (24)$$

   When $Z = 0$, in addition to always-takers with $T_w(0) = t$, $\mathbf{1}[T_w = t] = 1$ for compliers with

$T_w(0) = t < w = T_w(1)$. Thus,

$$\begin{aligned} E[\mathbf{1}[T_w = t] \times Y_w \mid Z = 0] =& P[T_w(1) = T_w(0) = t]E[Y_w(t) \mid T_w(1) = T_w(0) = t] \\ &+ P[T_w(1) = w, T_w(0) = t]E[Y_w(t) \mid T_w(1) = w, T_w(0) = t], \end{aligned}$$

which together with (24) establishes (19). Equation (22) follows from the same argument used to establish (24).

3. To show (20), note that monotonicity implies

$$\begin{aligned} E[Y_w \mid w > T_w \geq 1, Z = 1] &= E[Y_w(T_w(1)) \mid w > T_w(1) \geq 1] \\ &= E[Y_w(T_w(1)) \mid w > T_w(1) = T_w(0) \geq 1], \end{aligned}$$

since $P[T_w(1) = T_w(0) \mid 1 \leq T_w(1) < w] = 1$ under Assumption 6.

4. To show (21), note that

$$\begin{aligned} &E[Y_w(T_w(1)) \mid T_w(1) = T_w(0) \geq 1] \\ =&P[T_w(1) = T_w(0) = w \mid T_w(1) = T_w(0) \geq 1]E[Y_w(T_w(1)) \mid T_w(1) = T_w(0) = w] \\ &+ P[w > T_w(1) = T_w(0) \geq 1 \mid T_w(1) = T_w(0) \geq 1]E[Y_w(T_w(1)) \mid w > T_w(1) = T_w(0) \geq 1]. \end{aligned}$$

The fact that $E[Y_w(T_w(1)) \mid T_w(1) = T_w(0) = w] = E[Y_w \mid T_w = w, Z = 0]$ follows from equation (17) by noting that $T_1(1) = T_1(0) = 1$ if, and only if, $T_w(1) = T_w(0) = w$ because treatment is irreversible. The result that $E[Y_w(T_w(1)) \mid w > T_w(1) = T_w(0) \geq 1] = E[X_w \mid w > T_w \geq 1, Z = 1]$ follows from (20). Finally, monotonicity implies $E[\mathbf{1}[T_w = w] \mid Z = 0] = P[T_w(1) = T_w(0) = w]$ and, under IMCO, $E[\mathbf{1}[1 \leq T_w < w] \mid Z = 1] = P[w > T_w(1) = T_w(0) \geq 1]$. Thus, $\pi_w = P[T_w(1) = T_w(0) = w \mid T_w(1) = T_w(0) \geq 1]$.

Note that equation 15 uses $E[X \mid T_1 = 1, Z = 0]$ while equation 21 uses $E[Y_w \mid T_w = w, Z = 0]$. Because treatment is irreversible, conditioning on $T_1 = 1$ is equivalent to condition on $T_w = w$. In the case of equation 15, because $X$ does not vary across waves, this means that $E[X \mid T_1 = 1, Z = 0]$ can be computed only once even though $E[X \mid T_w(1) = T_w(0) \geq 1]$ varies with $w$. On the other hand, in equation 21, $E[Y_w \mid T_w = w, Z = 0]$ varies with $w$ even though the latent group does not. In practice, it's probably more practical to compute $E[Y_w \mid T_w = w, Z = 0]$ instead of $E[Y_w \mid T_1 = 1, Z = 0]$.