

# Registry-based randomized clinical trials in cardiology: opportunities and challenges



## Ensayos clínicos basados en registros en cardiología: oportunidades y retos

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### INTRODUCTION

The randomized clinical trial (RCT) has become the gold standard for evaluating clinical treatments thanks to its low selection bias and unknown confounders. However, good clinical practice guidelines and demands from regulatory agencies have become so elaborate over time that, basically, only big pharmaceutical companies have the resources to conduct large RCTs. Therefore, important questions raised by academic scientists could be impossible to test in clinical trials.

One way to circumvent these problems is to use the registry-based randomized clinical trial (RRCT) design. A RRCT uses the platform of an already-existing high-quality observational health registry as a case-report form for randomization and follow-up purposes. This design facilitates the randomization of a large number of patients over a short period of time, reduces costs to a fraction of the cost of conventional randomized clinical trials, and facilitates the follow-up of all eligible patients not enrolled in the study (table 1).<sup>1-4</sup>

### RRCT-SUITABLE REGISTRIES

Nearly all healthcare data are stored digitally today, which poses an excellent opportunity to use these data in a RRCT. However, healthcare records are often not structured in a way that allows useful data extraction. Today, disease-specific quality registries with full nationwide coverage are the most suitable ones as the basis for RRCTs, but this may change in the future. Our experience comes from using the Swedish Web-system for the Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) and its Swedish Coronary Angiography and Angioplasty Registry (SCAAR)<sup>5</sup> through which a large number of RRCTs have been conducted or are in ongoing phases (table 2).<sup>6-10</sup> The validation of registry data vs health records has an overall percent agreement of 96%.<sup>11</sup> The first pure RRCT was the TASTE trial where thrombus aspiration in patients with ST-segment elevation myocardial infarction (STEMI) was studied with mortality as the primary endpoint.<sup>1</sup> A large number of patients were rapidly included and with a limited budget by only using registries of baseline demographics, randomization, and endpoint collection in a prospective and randomized fashion. In this trial of a simple device intervention and a solid endpoint, the SWEDEHEART registry provided all the necessary steps to conduct a RCT (table 1). First, identify eligible patients and “flag” them with a pop-up window to the investigator appointed prior to the procedure. Secondly, open up

Table 1. Major functions for trial conduction provided by the registry

Major functions for trial conduction provided by the registry
Identification of eligible patients
Alert investigator of an eligible patient
Link to randomization module
Randomization
Collection of baseline and procedural characteristics from a registry (eCRF)
Presentation of additional trial-specific questions for eCRF
Identification of clinical endpoints (endpoint detection)
Clinical outcomes reporting
Reporting of characteristics of enrolled and non-enrolled patients from the overall population

eCRF, electronic case report form.

a randomization window with 2 questions: Have the inclusion/exclusion criteria been met? Has the patient given his consent to enter the study? If the answers to both these questions were positive, the patient was randomized and the result shown on the screen momentarily. Thirdly, both the baseline characteristics and the follow-up endpoints were collected from the registry. Furthermore, data on all of the unrecruited patients with complete baseline characteristics are collected. It is interesting to compare the TASTE to the TOTAL trial that examined thrombus aspiration using the traditional RCT design.<sup>12</sup> While the cost of the TOTAL trial was approximately €15000000 with 87 centers enrolling patients for 48 months on a 6-month follow-up, the cost of the TASTE trial was €500000 (3%!) with 30 centers enrolling patients for 33 months on a 42-month follow-up being the results nearly identical. In these circumstances of low complexity in both treatment and endpoints an RRCT is superior, in almost every aspect, to a traditional RCT.

### ADVANTAGES AND LIMITATIONS OF PURE RRCTS COMPARED TO TRADITIONAL RCTS

The major advantages of the RRCT design are: a) a broader and more representative population to clinical reality; in the TASTE and VALIDATE-SWEDEHEART trials 70% of all eligible patients were

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**Table 2.** Registry-based randomized clinical trials in the SWEDEHEART registry: completed, ongoing or in the pipeline

RRCT	Patients, N	Question	Dates
TASTE, Fröbert et al. <sup>1</sup> (2013)	7200	Thrombus aspiration in primary PCI	2013 + 2014
IFR-SWEDEHEART, Gotberg et al. <sup>6</sup> (2017)	2018	iFR vs FFR in stable angina or ACS	2017
VALIDATE-SWEDEHEART Erlinge et al. <sup>7</sup> (2017)	6006	Bivalirudin vs UFH for PCI in ACS	2017
DETO2X-AMI, Hofmann et al. <sup>9</sup> (2017)	6629	Oxygen therapy in MI	2017
FULL-REVASC, NCT02862119	4052	FFR-guidance in MI	Enrollment stopped after 1545 patients
PROSPECT-II, NCT02171065	900	Near-infrared spectroscopy in PCI	Presented, TCT 2020
IAMI, Fröbert et al. <sup>9</sup> (2017)	4400	Influenza vaccination after MI	Completed enrollment
SPIRRIT, NCT02901184	3200	Spironolactone for HFpEF	Ongoing
REDUCE, NCT03278509	6600	Beta-blocker post MI in patients with ejection fraction > 50%	Ongoing
ABC-AF, NCT03753490	6500	Biomarker score-based treatment vs standard care	Ongoing
MINOCA-BAT, NCT03686696	2048	ACEi/beta-blockers after MI with non-obstructive CAD	Ongoing
TACSI, NCT03560310	2200	Post-CABG ACS, ticagrelor	Ongoing
SWEDEGRAFT, NCT03501303	902	CABG grafting	Completed enrollment
Infinity-Swedeheart, NCT04562805	2400	Disengaging DES vs DES	Ongoing
DAPA-MI, NCT04564742	6400	SGLT2 inhibitor post-AMI	Ongoing
HELP-SWEDEHEART <sup>a</sup>	20000	<i>Helicobacter pylori</i> screening after AMI to prevent upper gastrointestinal bleeding (cluster-randomization)	Q2, 2021
SWITCH <sup>b</sup>	20000	Prasugrel or ticagrelor post-MI (cluster-randomization)	In the pipeline
BROKEN-Swedeheart, NCT04666454	1000	Optimal medical treatment for Tako-tsubo syndrome	In the pipeline

<sup>a</sup> Still unregistered; pilot study: NCT04289012.

<sup>b</sup> Still unregistered.

ACEi, angiotensin-converting enzyme inhibitor; AMI, acute myocardial infarction; ACS, acute coronary syndromes; CABG, coronary artery bypass graft; CAD, coronary artery disease; DES, drug-eluting stent; FFR, fractional flow reserve; HFpEF, heart failure with preserved ejection fraction; iFR, instantaneous wave-free ratio; MI, myocardial infarction; EFPCI cabg SGLT2, sodium-glucose cotransporter-2; PCI percutaneous coronary intervention; TCT, Transcatheter Cardiovascular Therapeutics conference; UFH, unfractionated heparin.

included<sup>1,7</sup>; b) clinically significant endpoints were included, and not multiple composite weak or surrogate endpoints; c) long-term follow-up periods, actually life-long follow-ups, if applicable; d) thanks to random selection, bias and confounding factors are reduced to a minimum; e) significantly lower costs; f) rapid inclusion of a large number of patients; and g) initiated and conducted by independent academic researchers with no links to the industry.

The limitations are: a) open label design with a risk of biased endpoint reporting; b) rare, unexpected events may be missing, and serious adverse event reporting may be difficult; c) events are, for the most part, not adjudicated, which may result in variable data quality; d) difficulties having central chemical analysis and biobanking; e) long-term oral drugs can be difficult to distribute and follow; and f) lack of or limited site monitoring (figure 1).

Depending on the limitations of the registry used, need for treatment escalation or endpoint complexity the RRCT can be complemented with different traditional trial elements resulting in a hybrid RRCT (figure 2).

## DEVELOPMENT OF RRCTS

In the SORT OUT series of coronary stent trials, baseline demographics and endpoint screening were conducted using a registry approach. However, randomization took place using different

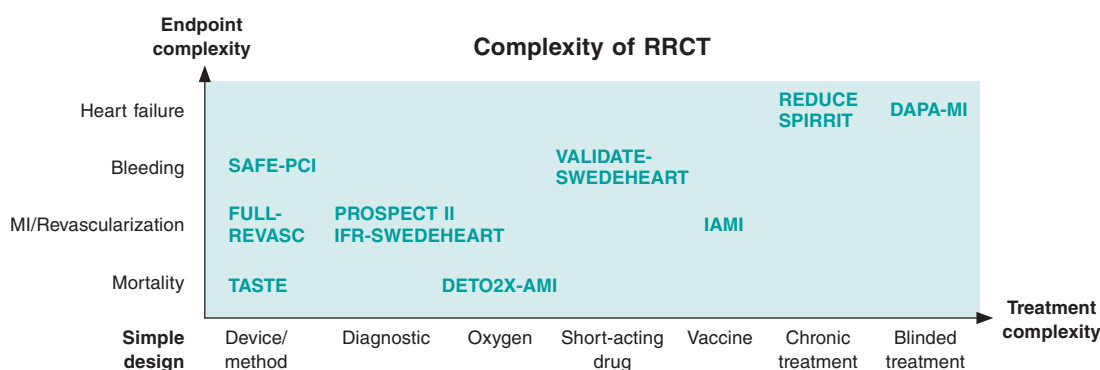
approaches (telephone allocation service, internet-based randomization systems), and endpoints were centrally adjudicated.<sup>13</sup> In the SAFE-PCI study, randomization was performed outside the registry obtaining additional clinical information and adjudication to the registry data.<sup>14</sup>

In the VALIDATE-SWEDEHEART trial, 2 short-acting IV anti-thrombotic agents (bivalirudin and heparin) were assessed using the RRCT approach. As far as we know, this was the first pharmaceutical RRCT ever conducted.<sup>7</sup> In a pharmaceutical trial the requirements from the medical regulatory authorities are more demanding even if the drugs have been approved and used for decades. Furthermore, we realized that our registry did not capture bleeding complications satisfactorily. Therefore, we added phone calls after 7 to 180 days followed by the central adjudication of bleeding complications and MI, limited serious event reporting, and data on the entire index hospitalization. Thanks to the simplicity of the trial, 25 centers were able to enroll over 6000 patients with MI over 2 years. Some large centers enrolled more than 1000 patients (figure 2, table 2).

In the IFR-SWEDEHEART trial the instantaneous wave-free ratio diagnostic modality was evaluated. The complexity of the intervention was low, but the composite endpoint included MI and unplanned revascularization.<sup>6</sup> Although the endpoints were found in the registries, data were collected from medical records from the centers and adjudicated by a central committee.

Classic RCT	RRCT	Observational Registry
Randomized	Randomized	Non-randomized
Causality	Causality	Hypothesis generating
Cumbersome screening	Registry screening and alert to local investigator	Registration of eligible patients
Narrow selection (5%)	Broad selection (50%-70%)	All-comers
Endpoint adjudication	Registry endpoints ± adjudication	Registry endpoints
Expensive	Low cost	Minimal cost
Blinded	Open label/single blinded	Open label
Extensive on-site monitoring	Selected monitoring	Registry monitoring
SAE reporting	Selected SAE reporting	None
Cumbersome screening failed reporting	Report of all unrecruited eligible patients	Registry of an entire disease population
Limited generalizability	High degree of generalizability	Real-world patients
Slow recruitment	Rapid recruitment	Continuous recruitment

**Figure 1.** Comparison of traditional randomized clinical trials (RCTs), registry studies, and registry-based randomized clinical trials (RRCT). Classical RCTs are the gold standard of clinical research, but they have limitations because they are very expensive, selective, and a cumbersome process. Retrospective registry studies can be conducted much cheaper, and may be more representative of the real world, yet they are always hampered by unknown confounders. An RRCT can profit from the best parts of these modalities. SAE, serious adverse event.



**Figure 2.** Simple versus complex registry-based randomized clinical trials (RRCT). The purest RRCT examines a simple therapy like a thrombus aspiration device and has a robust endpoint like mortality. When the complexity increases for either treatment or endpoint, then additions to the RRCT design have to be made. These additions could be phone calls, central adjudication, or even blinded treatment with placebo. This increases complexity and costs, but the registry may still be the basis for the trial and facilitate performance. MI, myocardial infarction.

In the DETO2X-AMI trial the endpoint was mortality, which does not need adjudication; however, the oxygen of the procedure had to be administered to the patient in a single blinded fashion adding some extra complexity to the study<sup>8</sup> (figure 2, table 2). Similarly, the influenza vaccine study conducted post-MI (IAMI trial) needed blinded treatment.<sup>9</sup> Furthermore, other countries without the SWEDEHEART registry structure were needed to get a sufficient number of patients, which resulted in a parallel randomization module and electronic case report forms (figure 2, table 2).<sup>9</sup>

There are 2 ongoing RRCTs with chronic oral treatment and a composite endpoint of death and hospitalizations due to heart failure: the REDUCE (beta-blocker post-MI, NCT03278509) and the SPIRRIT (Spironolactone for Heart Failure with Preserved Ejection Fraction, NCT02901184). However, despite the complex treatment and endpoint of both of them, they rely nearly only on registries. The treatment is randomized in the registry, prescribed, and then followed by the Swedish Prescribed Drug Register. Hospitalizations due to heart failure are collected from the National Patient Register where this diagnosis has proven to have a high validity in previous studies.

### FUTURE POSSIBILITIES OF THE RRCT CONCEPT

So far, the RRCT technology has mostly been used for the assessment of devices or generic drugs that have been used for decades often with results that the treatment examined has been redundant, as it has been the case with the TASTE and VALIDATE-SWEDEHEART trials. Sometimes, as it occurred with the IFR-SWEDEHEART study, a new diagnostic procedure proves to be non-inferior to the current standard.<sup>6</sup> This resulted in an IA recommendation for the instantaneous wave-free ratio in the clinical practice guidelines. In general, RRCTs have been deemed unsuitable by the medical regulatory authorities for first approval, but this is about to change. The INFINITY trial (NCT04562805) is examining a new type of stent capable of disengaging its metal struts after half a year. This is a currently ongoing RRCT whose objective is to support an approval given by the US Food and Drug Administration (FDA). Demographics, randomization, and endpoint follow-up are already taken care of by the SWEDEHEART registry, still a phone call at 1 month and 1 year combined with central adjudication was added.

The first study, that has been analyzing an expanded use for an oral drug, is the DAPA-MI study (NCT04564742) where dapagliflozin is being tested for post-MI patients with reduced ejection fraction but without diabetes. The registry is the basis of the study, yet visits have been added to dispense the blinded medication. The study is sponsored by AstraZeneca and intends to develop new more cost-efficient ways to conduct phase III trials. The study profits from 2 countries with nationwide MI registries, the UK and Sweden, with their MINAP<sup>16</sup> and SWEDEHEART<sup>5</sup> registries, respectively.

In Europe, the European Society of Cardiology has mostly relied on surveys to register different heart conditions. These are valuable, but they only give us a snapshot of a short timeframe and the selection of patients is unclear and may not be representative of the real world. However, a new initiative called EuroHeart<sup>17</sup> has been trying to establish a common basic structure for continuous cardiac registries that could be used by any countries. One of its objectives is to facilitate conducting RRCTs in several European countries making the results more representative and allowing larger studies being conducted more rapidly.

### CLUSTER-RANDOMIZED RRCTs

Cluster randomization design simplifies enrollment and does not often require signed informed consent forms, only general information about the ongoing study. It facilitates the recruitment of nearly all patients from a region during a certain period of time and it basically uses a cross-over design. In the HELP-SWEDEHEART trial—still not registered—20 000 patients diagnosed with MI in the SWEDEHEART registry will, based on hospital data, be cluster-randomized in a crossover design to receive *Helicobacter pylori* screening and, if they test positive, be recommended eradication therapy. The primary endpoint is upper gastrointestinal bleeding, which is collected from the National Patient Register. The still unregistered SWITCH trial is planning to investigate prasugrel compared to ticagrelor for the treatment of patients hospitalized due to MI with the composite endpoint of death, MI or stroke collected from the National Patient Register and the National Cause of Death Registry. A total of 4 Swedish regions will be randomized in blocks to standard use of either prasugrel or ticagrelor over 2 years.

In conclusion, RRCTs combine some of the best parts of the classical RCT design and traditional registries when conducting large, randomized, real-world, representative, and cost-effective clinical studies. They give academic researchers an opportunity to obtain important clinical answers that would have never been funded by industry.

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