

SUPPLEMENTAL MATERIAL

Appendix

PARTICIPATING CENTERS in SCAAR

Borås Hospital, Sweden.

Capio, St. Görans Hospital, Sweden.

Danderyd University Hospital, Sweden.

Eskilstuna Hospital, Sweden.

Falun Hospital, Sweden.

Gävle Hospital, Sweden.

Halmstad Hospital, Sweden.

Helsingborg Hospital, Sweden.

Jönköping Hospital, Sweden.

Kalmar Hospital, Sweden.

Karlskrona Hospital, Sweden.

Karlstad Hospital, Sweden.

Karolinska Solna and Huddinge University Hospitals, Sweden.

Kristianstad Hospital, Sweden.

Linköping University Hospital, Sweden.

Sahlgrenska University Hospital, Sweden.

Skövde Hospital, Sweden.

Skåne University Hospital, Sweden.

Sunderby Hospital, Sweden. Sundsvall Hospital, Sweden.

Södersjukhuset (Stockholm South General Hospital), Sweden.

Trollhättan Hospital (NÄL), Sweden.

Umeå University Hospital, Sweden.

Uppsala University Hospital, Sweden.

Västerås Hospital, Sweden.

Örebro University Hospital, Sweden.

Data S1.

DESCRIPTION OF THE SCAAR/SWEDEHEART REGISTRIES

The SWEDEHEART registry

The Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies (SWEDEHEART) was established in December 2009 after merging of the national registry of acute cardiac care (RIKS-HIA), the Swedish coronary angiography and angioplasty registry (SCAAR), the Swedish heart surgery registry and the national registry of secondary prevention (SEPHIA). RIKS-HIA was developed in 1990 and was established as a National quality registry in 1995. SEPHIA was added to RIKS-HIA in 2005 to register effects of secondary prevention efforts in patients with acute myocardial infarction. SCAAR was established in 1998 after a merge of a Swedish national angioplasty registry and Swedish national coronary angiography registry that were both initiated in the early 1990s by hospitals which at that time performed coronary angiographies and PCIs. The Swedish heart surgery registry was formed in 1992.

Organization and funding

SWEDEHEART is managed by a steering group, consisting of the chairmen of the working groups of the individual registries and representatives from the Swedish Heart Association and the Swedish Society of Cardiac Nursing. Uppsala Clinical Research Center (UCR) has developed the web based version of the registry and is responsible for project management, administration, monitoring, quality controls, and statistical reports. The registry is financed by the Swedish Association of Local Authorities and Regions (the public health care provider), and is supported by the Swedish Heart Association, the National Board of Health and Welfare and the Swedish Heart and Lung Foundation. Participating hospitals are not reimbursed by SWEDEHEART and costs of local data entry are covered by internal budgets.

Data

SWEDEHEART includes patients admitted to hospital because of symptoms suggestive of an acute coronary syndrome (ACS), and patients who undergo coronary angiography/angioplasty or heart surgery. The registry enrolls approximately 80,000 cases each year: 30,000 with ACS, 40,000

undergoing coronary angiography or angioplasty, and 7,000 undergoing heart surgery. The registry is web-based with all data registered on-line directly by the caregiver and transferred in an encrypted format to a central server. During registration the whole process of care is kept together in one record even if the patient is transferred between different units and hospitals. The technical platform, OpenQreg, is published as open source software that can receive data via the Internet or from other databases and electronic patient journals. The platform is in direct contact with the Swedish National Population Registry for immediate access to personal data and deaths.

For patients admitted to hospital because of symptoms suggestive of an ACS information is collected prospectively for 106 variables and include patient demographics, admission logistics, risk factors, past medical history, medical treatment prior to admission, electrocardiographic changes, biochemical markers, other clinical features and investigations, medical treatment in hospital, interventions, hospital outcome, discharge diagnoses and discharge-medications. The registry also includes a detailed description of angiographic findings, procedures, type of stenosis, type of stent, antithrombotic treatment, and complications. The system has an interactive method for registration of restenosis and stent thrombosis. Detailed information about every previously implanted stent anywhere in the country is presented and a mandatory question about existence of any form of restenosis or stent thrombosis has to be answered. Every hospital in Sweden providing the relevant services participates in the SWEDEHEART registry.

Patient identification

Every Swedish citizen has a unique personal identification number which together with name, address and hospital identity is included in the registry. The use of personal identification number enables merging of the SWEDEHEART database with the National Cause of Death Register, which includes information about the vital status of all Swedish citizens, and the National Patient Registry, which includes diagnoses at discharge for all hospital stays in Sweden. All patients are informed about their participation in the registry and the follow-up, and have the right to decline participation. Every merge of registries is approved by the National Board of Health and Welfare, the Swedish Data Inspection

Board and the ethical committee at Uppsala University. After merging of the registries, researchers have access to hospital identity but not to patient identity.

Data quality

Uppsala Clinical Research Center provides manuals, education and technical advice, including a telephone help desk for all users of the registry. The system has error checking routines for range and consistency. Definitions are easily available when data are entered. To ensure the correctness of the data entered a monitor annually visits about 20 hospitals and compares data entered into the SWEDEHEART with the information in the patients' records from 30–40 randomly chosen patients in each hospital. When 637 randomly chosen computer forms from 21 hospitals containing 38 121 variables were reviewed in 2007, there was a 96.1% (range: 92.6%-97.4%) agreement. To reach a high degree of completeness a majority of variables are mandatory and each hospital can monitor data completeness. The system provides all users with an array of on-line interactive reports regarding changes of processes of care and outcome in direct comparison with other hospitals. The SCAAR registry also works as a clinical tool as it displays detailed information about any previously performed intervention. Following a coronary procedure two reports summarizing the findings and intervention performed are printed; one for the patient and one for the patient's clinical files. The second part includes a request to the ward to report potential complications post-PCI. The registry captures 100% of the patients undergoing angiography, angioplasty or heart surgery.

Use of SWEDEHEART data

The main purpose of the registry is to support the improvement of care and evidence based development of therapy of coronary artery disease by providing continuous information on care needs, therapy and results of therapy and changes within a hospital as well as in comparison to other hospitals. The long-term goals are to contribute to decreased mortality and morbidity among the patients and to increase the cost effectiveness in coronary care. A national, regional and county based report is presented on a yearly basis showing all these levels openly concerning a large number of variables. The registry compares performance of participating hospitals and different treatment

modalities and medical devices. The results, especially regarding differences between different hospitals and the adherence to national guidelines, have also been associated with attention and discussion in different media and authorities, which have further contributed to the improvements in care. In addition, many hospitals are engaged in collaborations on quality development projects, which are supported by the on-line interactive reporting system as a continuous quality control instrument. By giving each hospital an opportunity to compare its treatments and results over time and with other hospitals, the registry has proven to be a powerful tool for improvements both locally and nationally. SWEDEHEART and its originally four registries have, so far, been the source of more than 100 original scientific papers of which several have been in high-ranking journals.

Randomized Registry Clinical Trials (RRCT) in SWEDEHEART

Several large multi-center randomized clinical trials have been fully conducted within the SWEDEHEART registry. In the TASTE trial (Thrombus Aspiration in ST-elevation in Scandinavia), 7200 patients were included to test the effect of thrombus aspiration on mortality in ST-elevation myocardial infarction. Other RRCTs conducted within the SWEDEHEART registry include DETOX (DETermination of the role of OXYgen in suspected Acute Myocardial Infarction trial; N=6629), VALIDATE (Bivalirudin versus heparin in non-ST and ST-segment elevation myocardial infarction-a registry-based randomized clinical trial in the registry; N=6,606), and iFR (Instantaneous Wave-free Ratio versus Fractional Flow Reserve to Guide PCI; N=2,037).

MULTIPLE IMPUTATION OF MISSING DATA

Missing data are frequent in observational studies, and in the presence of missing data statistical modeling using only subjects with complete data for all variables (“complete-case” analyses) may be biased and inefficient. In accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) consensus document we imputed missing data using multiple imputation, under the assumption that data were missing at random. The imputation protocol consisted of the chain-equation method¹ with 20 data sets and a predictive-mean matching algorithm. We used the same covariates in the imputation protocol as in the main analysis with addition of an event indicator. We imputed 20 data sets with 10, 50 and 100 cycles between the outputs. We tested the adequacy of the iterations (convergence) by visual inspection of trace plots for different chains which showed no apparent trends for the imputed values between the imputation models. We then decided to use 100 cycles in the final model. Continuous variables were imputed by ordinary least squares regression whereas binary variables were imputed using logistic regression and categorical variables by multinomial logistic regression. The following variables had missing data and were imputed: diabetes, hypertension, hyperlipidemia, smoking status, previous myocardial infarction, previous PCI, previous CABG, extent of coronary artery disease, ASA, clopidogrel, ticagrelor, prasugrel, glycoprotein inhibitors, unfractionated heparin, bivalirudin, thrombolysis, warfarin, cardiogenic shock, complete revascularization. The following variables were included in the imputation model as regular variables: age, gender, year of intervention, hospital, previous myocardial infarction, treated vessel, arterial access site, indicator of missing data, vital status. The imputation procedure and the subsequent analyses were performed according to the Rubin’s protocol² using Stata software³ (version 15.0, StataCorp, College Station, TX).

Propensity score

We used a propensity score model to adjust for differences in patient characteristics. The significant predictors of thrombus aspiration and PCI for each patient were identified by fitting a logistic regression model with (1) a binary dependent variable representing thrombus aspiration and PCI and

(2) with candidate variables consisting of the patient-related predictors of the type of therapy used. The following variables were used for estimation of propensity score: age, gender, diabetes mellitus, hypertension, hyperlipidemia, smoking status, previous PCI, previous CABG, previous myocardial infarction, extent of CAD, complete revascularization, treatment with aspirin, treatment with clopidogrel, treatment with ticagrelor, treatment with prasugrel, treatment with GP2b3a-blocker, treatment with unfractionated heparin/LMWH, treatment with bivalirudin, treatment with thrombolysis, treatment with warfarin, procedural success, puncture site, treatment with drug eluting stent, cardiogenic shock.

Supplemental References:

1. van Buuren S. Multiple imputation of discrete and continuous data by fully conditional specification. *Statistical methods in medical research*. 2007;16:219-42.
2. Rubin DB. Inference and Missing Data. *Biometrika*. 1976;63:581-590.
3. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine*. 2011;30:377-99.