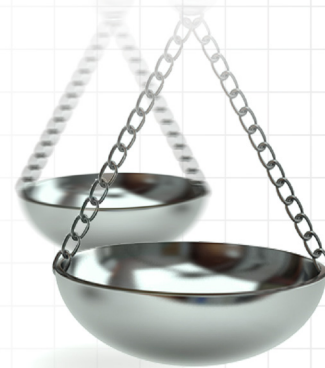




Targeted identification of adverse events in coronary artery disease patients based on patient-reported outcomes

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Aim: Can focusing the adverse events search to patients with poor patient-reported outcome help in targeting adverse event detection? **Patients & methods:** Coronary artery revascularization patients of the Kuopio University Hospital from June 2012 to August 2014 categorized into those with clinically significant improvement (15D score change ≥ 0.015 , $n = 81$) or deterioration (change ≥ -0.015 , $n = 64$) in post-intervention health-related quality of life. **Results:** Major complications (27 vs 9%, $p = 0.004$) or post-intervention infections (16 vs 5%, $p = 0.031$) were more common among those with deteriorated score. They also tended to have more cardiovascular (19 vs 9%, $p = 0.071$) and minor complications (16 vs 7%, $p = 0.118$). **Conclusion:** Patient-reported outcomes may potentially help in targeting the adverse events search so that a larger number of adverse events can be identified for efficient learning from them.

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Keywords: cardiology/cardiovascular • comparative safety • patient-reported outcomes

To be able to continuously improve healthcare, identification of adverse events and learning from them is important. Voluntary reporting systems have gained popularity during recent years but underestimate the real number of adverse events as only a small percentage of them are usually reported [1,2]. The same seems to apply, at least in Finland, to the use of International Classification of Diseases codes generated for reporting of adverse events as they in practice appear to be rarely recorded.

Reviewing patient records is currently considered the best way to detect adverse events, but it is tedious, time consuming and often not very productive. To advance the identification of adverse events from patient records, the Institute for Healthcare Improvement [3] has developed the Global Trigger Tool which is currently considered as the golden standard for detecting adverse events in patient safety research [4–7]. Global Trigger Tool aims to narrow down, by identifying certain keywords associated with safety incidents, the number of full patient records that needs to be reviewed [8].

An alternative or complementary approach could be to focus the searching of adverse events to patients with poor patient-reported treatment outcomes (PROs). Adverse events usually affect the subjective state of health negatively and, consequently, are often reflected in poor PROs. As utility of treatment is currently often monitored by using PROs, data collected for this purpose could possibly also be used for the identification of patients that are more likely than average to have suffered an adverse event.

Our hospital collects routine PRO data in the form of health-related quality of life (HRQoL) measurements which makes it also possible to easily identify patients in whom the PRO does not improve following treatment. We tested in a pilot study on coronary artery disease patients whether there is an association between poor PROs

and adverse events and/or comorbidities in the hope that such an approach would facilitate focusing the search for adverse events on the right patients.

Patients & methods

Study design & setting

Our hospital has collected HRQoL data with the 15D instrument [9–11] as part of its routine practice since autumn 2011. Currently such data is collected in 16 distinct patient groups. The participants of this study were cardiac patients admitted for coronary revascularization therapy (coronary artery bypass grafting or percutaneous coronary intervention). They were, from June 2012 to August 2014, asked, as part of routine clinical practice, to fill in the 15D questionnaire at baseline and 12 months after the revascularization procedure.

The 15D instrument is a generic, self-administered HRQoL questionnaire. It consists of 15 dimensions (mobility, vision, hearing, breathing, sleeping, eating, speech, excretion, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity) with five ordinal levels. The 15D instrument produces single index scores which range from 0 to 1. It can generate over 30 billion different health states. The valuation system of the 15D used in this study is based on a set of population-based preferences [9–11]. The minimal important difference (MID) in the 15D score has been reported to be ± 0.015 [12].

Patients having returned both the baseline and the 12-month questionnaires were categorized, based on the observed changes in their HRQoL scores after the treatment, to those with a clinically significant improvement (change in the 15D score ≥ 0.015), or a clinically significant deterioration (change in the 15D score ≤ -0.015) [12]. Patient records of both groups were then reviewed for possible comorbidities, both before and after the intervention and adverse events during the follow-up by two experienced investigators who were unaware of the treatment outcome.

Adverse events were categorized into clinically significant (e.g., those requiring reoperation, extended hospital stay or rehospitalization, neurologic complications with devastating consequences such as stroke, etc.), or minor (e.g., uncomplicated wound infections) adverse events (Table 1). In case a patient had encountered both a major and a minor complication, he/she was classified only into the major complication category. All reported comorbidities were noted and categorized into those deemed clinically significant from a HRQoL point of view (e.g., neurologic comorbidities with a physical handicap or severe heart or lung conditions restricting even light physical exercise, etc.) or nonsignificant (hypertension, uncomplicated diabetes etc.; see Table 1).

As our university hospital serves as a tertiary care center and is responsible for invasive cardiac interventions of also some hospital districts outside of its immediate catchment area, post-intervention treatment of some of the cardiac patients took place in other hospitals. To ensure that we had access to patient records covering the whole secondary care treatment path of the patients, only patients whose entire secondary care treatment took place in this university hospital, were included in the analysis.

Statistical analyses

Descriptive statistics for demographic data are presented using frequencies and percentages. Results are presented as means with 95% confidence intervals. Differences between the groups of interests were tested by ordinary least square regression analysis. Differences between groups with a positive and a negative PRO were tested in a univariate logistic regression model using age, sex, operation type, number of all comorbidities and the absence or presence of significant comorbidities as independent variables. Multivariable logistic regression was performed using the same variables as above, except for the number of comorbidities because of its collinearity with the presence or absence of significant comorbidities. The observed HRQoL score changes were normally distributed and associations between various characteristics and HRQoL changes were tested by linear regression. All statistical analyses were conducted by STATA 12.0 (Stata Corp. LP, TX, USA) or SPSS 19 (IBM SPSS statistics for Windows, NY, USA).

Results

During the study period, the mean 15D score change for all 378 revascularized patients having answered both the baseline and the 12-month 15D questionnaire was 0.016 (0.022 for women and 0.014 for men, $p = 0.442$). Age was inversely associated with the 15D score gain (Table 2).

Altogether 145 patients with a clinically significant 15D score change lived in the immediate catchment area of the hospital. 81 (55.9%) of them had a positive MID and 64 (44.1%) a negative MID. The group with a minimal clinically significant negative 15D score change had, on average, more adverse events or comorbidities than the

Table 1. Adverse events/complications and comorbidities in the study population (see text for details).

Adverse event type	Clinically significant	Minor/clinically nonsignificant
Cardiovascular complication	Re-operation required	Postoperative hematoma in groin
	Extended hospital stay or rehospitalization	Arrhythmia
	Neurologic complication (stroke)	Postoperative pneumothorax
	Stent thrombosis during follow-up	Postoperative atrial fibrillation
	Myocardial infarction	–
	Embolus	–
		–
Infection	Sternum wound infection	Operation wound excretion
	Sternum wound revision	Other wound infection
	Sternum wound dehiscence	–
	Sepsis	–
	Urosepsis	–
Other complication	Failed revascularization	Postoperative ileus
	Postoperative mental confusion	Ileus
	Hip luxation	Rash (Plavix)
	Peroneal paresis	–
Comorbidities in the study population	Neurologic comorbidities with a physical handicap	Hypertension
	Severe heart condition/heart failure	Uncomplicated diabetes
	Severe lung condition	Asthma
	Claudication	Cancer having been treated earlier
	Spinal stenosis	Tinnitus
	Chronic obstructive pulmonary disease	Benign musculoskeletal disorders
	Spinal disc herniation during follow-up	Benign prostatic hyperplasia
	New cancer during follow-up	Eye pain
	Continuous pain	Collapse
	Ulcerative colitis	Rheumatic disorder
	Asbestosis	Pneumonia
	Stroke or other cerebrovascular incident	Parkinson's disease
	Recurrent pneumonia	Metabolic syndrome
	Complicated diabetes	Need for pacemaker during follow-up
	Symptomatic lower limb atherosclerosis	Chronic atrial fibrillation

Table 2. Characteristics of the total population (n = 378) and mean 15D score change during the 12-month follow-up.

Population	n (%)	Mean 15D score change (95% CI)	Least square difference (95% CI)	p-value ¹
Men	303 (80.2)	0.014 (0.005–0.023)	(Reference)	
Women	75 (19.8)	0.022 (0.005–0.039)	0.008 (-0.013–0.029)	0.442
CABG	209 (55.3)	0.029 (0.019–0.040)	(Reference)	
PCI	169 (44.7)	-0.001 (-0.014–0.011)	-0.031 (-0.048 to -0.015)	<0.001
Age under 60	89 (23.5)	0.027 (0.010–0.044)	(Reference)	
Age 60–74.9	203 (53.7)	0.018 (0.009–0.029)	-0.009 (-0.029–0.012)	0.412
Age 75 and over	86 (22.8)	-0.004 (-0.025–0.017)	-0.031 (-0.056 to -0.007)	0.011
No MID	73 (19.3)	0.0004 (-0.001–0.002)	(Reference)	
Positive MID	185 (48.9)	0.080 (0.073–0.088)	0.080 (0.068–0.922)	<0.001
Negative MID	120 (31.8)	-0.075 (-0.083 to -0.066)	-0.075 (-0.088 to -0.062)	<0.001

¹Statistical significance of difference estimated by ordinary least squares regression.

CABG: Coronary artery bypass grafting; MID: Minimal important difference; PCI: Percutaneous coronary intervention.

Table 3. Differences between positive and negative minimally important difference. size changes in health-related quality of life.

Groups	n (%) n = 145 (100.0)	MID, n (%)		Unadjusted			Adjusted [†]		
		Positive n = 81 (55.9)	Negative n = 64 (44.1)	OR	95% CI	p-value [‡]	OR	95% CI	p-value [‡]
Mean age (range)	66.7 (47–90)	65.4 (47–89)	68.3 (49–90)	0.967	0.932–1.003	0.071	0.966	0.928–1.005	0.083
Men	110 (75.9)	58 (71.6)	53 (81.3)	1.000	(Reference)		1.000	(Reference)	
Women	35 (24.1)	23 (28.4)	12 (18.7)	1.718	0.778–3.794	0.180	2.751	1.112–6.805	0.028
Comorbidities									
0	10 (6.9)	7 (8.6)	3 (4.7)	1.000	(Reference)		Omitted due to collinearity [§]		
1	29 (20.0)	19 (23.5)	10 (15.6)	0.814	0.172–3.853	0.796			
2	44 (30.3)	30 (37.0)	14 (21.9)	0.918	0.206–4.091	0.911			
3	24 (16.6)	11 (13.6)	13 (20.3)	0.363	0.075–1.748	0.206			
4	22 (15.2)	7 (8.6)	15 (23.4)	0.200	0.039–1.014	0.052			
≥5	16 (11.0)	7 (8.6)	9 (14.1)	0.333	0.062–1.779	0.199			
Significant comorbidities	46 (31.7)	11 (18.5)	31 (48.4)	0.242	0.115–0.509	<0.001	0.215	0.097–0.476	<0.001
Operation type									
PCI	96 (66.2)	51 (63.0)	45 (70.3)	1.000	(Reference)				
CABG	49 (33.8)	30 (37.0)	19 (29.7)	1.393	0.691–2.807	0.352	1.332	0.168–2.868	0.464

[†]Adjusted logistic regression age, sex and significant comorbidities.

[‡]Statistical significance of difference estimated by unadjusted and adjusted logistic regressions.

[§]Significant comorbidities and number of comorbidities. Spearman correlation was 0.507. Because of collinearity, a number of comorbidities were excluded to adjusted logistic regression model.

CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention.

group with clinically significantly improved 15D score. The patients with a clinically significant positive 15D score change were on average 3 years younger than those with a negative change (65.4 vs 68.3 years, $p = 0.071$; Table 3). The proportion of women was somewhat higher in the group with a positive change than in the group with a negative change, but the difference did not reach statistical significance (28.4 vs 18.8%, respectively, $p = 0.180$).

Of the patients with a clinically significant negative change in their 15D score, 26.6% had encountered a major complication compared with 8.6% of those with a positive treatment result ($p = 0.004$; see Figure 1A). The same was true for post-intervention infections (15.6 vs 4.9%, respectively, $p = 0.031$; see Figure 1B). Patients with a poor PRO also tended to have more often minor complications (15.6 vs 7.4%, respectively, $p = 0.118$; see Figure 1A) and cardiovascular complications (18.8 vs 8.6%, respectively, $p = 0.071$; see Figure 1B) but the differences were not statistically significant. There were no significant differences in the number of comorbidities between the groups. However, comorbidities which were deemed clinically significant from a HRQoL perspective were significantly more frequent in the group with poor PRO (18.5 vs 48.4%, $p < 0.001$; see Table 3). The association between adverse events and clinically significant 15D score change, nevertheless, remained after adjusting for comorbidities (Table 3).

The mean 15D change was negative both in patients with minor (-0.013, 95% CI: -0.067–0.419) or major adverse events (-0.029, 95% CI: -0.061–0.004; see Table 4). Furthermore, in patients with cardiovascular or infectious complications, the mean 15D score change was always negative although the difference, compared with patients without those complications, reached statistical significance only in the case of major complications and complications that were deemed to be unrelated to the revascularization therapy. Patients with significant comorbidities also showed a statistically significant deterioration in their mean 15D score (-0.025, 95% CI: -0.173–0.182) compared with the rest of the patients (Table 4).

Discussion

According to the results of this pilot study on coronary artery disease patients, there is a clear negative association between adverse events and HRQoL gain in patients undergoing coronary revascularization therapy. This reflects the 15D instrument's sensitivity to detect factors which affect the overall subjective state of health negatively. Partly the poor PRO can be explained by the higher number of comorbidities in the group with a negative outcome.

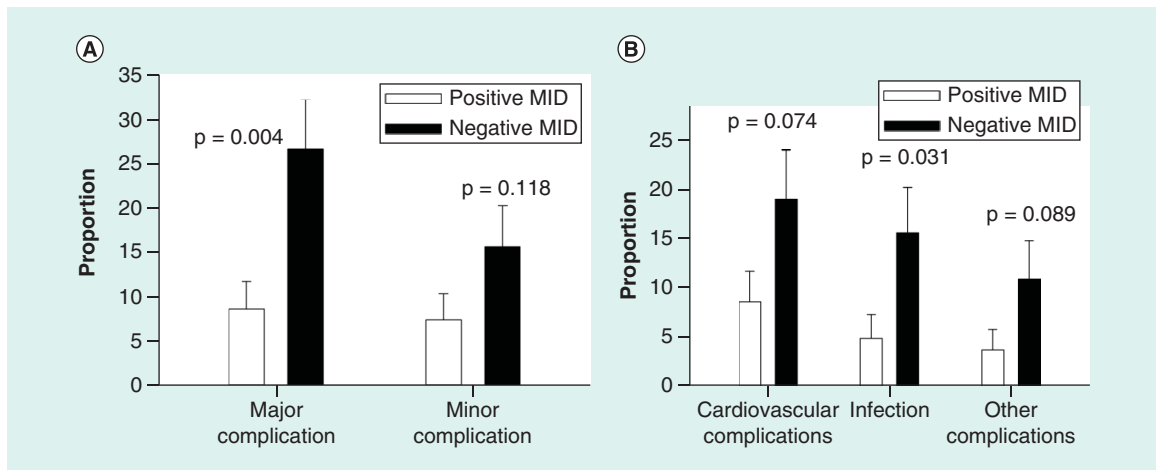


Figure 1. Percentages of patients with complications. (A) Major and minor complications and (B) cardiovascular complications, infections and other complications among those who experienced a clinically significant improvement (positive MID) or deterioration in health-related quality of life (negative MID) after coronary artery revascularization procedure. Significance of differences between positive and negative MID groups were calculated by ordinary least square univariate regressions. MID: Minimally important difference.

However, the statistically significant association between the adverse events and negative clinically significant 15D score change remained after adjusting for comorbidities.

Using the PRO of treatment as measured by the change in HRQoL could, according to our results, be a complementary approach for targeting the search for adverse events to those patients most likely to have encountered them. Identifying and measuring harm have been seen as core patient safety goals and the identification of vulnerabilities is necessary to learn from mistakes and to be able to take corrective action [13].

A limitation of the study is the fact that our preliminary findings are based on a small number of patients and only on coronary artery disease patients. The findings should thus be considered as tentative. As the 15D seems to react also to the occurrence of major infections, it is likely to help detect a wide range of unreported adverse events and also other than those directly related to the intervention. As HRQoL measurements are currently a fundamental part of routine comparative effectiveness analyses in our university hospital, they could, in addition to monitoring the effectiveness and cost-effectiveness of treatment, also be used to help focus the detection of adverse events to the right patients. Most likely, our approach could also utilize data obtained with other HRQoL instruments, but currently we have no results to substantiate such a claim. Furthermore, the generalizability of our results to other centers or settings needs to be established in future studies. The more adverse events we are able to identify, the more we can learn from them and thus develop safer and more effective hospital practices. Furthermore, analysis of patients with a positive or a negative HRQoL change can hopefully in the future improve the selection of patients most likely to benefit from revascularization therapy and, on the other hand, the identification of those that are prone to develop complications and comorbidities and, thus unlikely to gain from revascularization.

A strength of this pilot study is the fact that the findings are based on real-life data routinely collected in the hospital, not on highly selected patients usually seen in randomized controlled trials. Consequently, our results can probably be generalized also to other settings but further studies are needed to see whether similar results can also be obtained in other patient groups.

Conclusion

Poor effectiveness of treatment, as judged by a PRO, is often associated with adverse events. Using routinely collected PRO data may help target the search for adverse events to the right patients, and may potentially reveal a larger number of adverse events than currently used approaches. This enables more targeted improvement of healthcare processes. In the future, wider use of HRQoL measurements for the detection adverse events could be a new approach for harm reduction in healthcare.

Table 4. Mean (95% CI) 12-month 15D score change in the various subgroups of the patient material.

Groups	n (%)	Mean 15D change (95% CI)	Least square difference (95% CI)	p-value [†]
Women	35 (24.1)	0.031 (0.002–0.061)	(Reference)	–
Men	110 (75.9)	0.006 (-0.011–0.023)	0.025 (-0.009–0.059)	0.154
Operation type:				
– PCI	96 (66.2)	0.003 (-0.015–0.021)	(Reference)	–
– CABG	49 (33.8)	0.030 (0.004–0.056)	0.027 (-0.004–0.058)	0.089
Age under 60	45 (31.0)	0.024 (-0.003–0.051)	(Reference)	–
Age 60–74.9	63 (43.5)	0.020 (-0.001–0.182)	-0.003 (-0.038–0.031)	0.842
Age 75 and over	37 (25.5)	-0.016 (-0.047–0.016)	-0.039 (-0.079–0.001)	0.048
No minor complications	129 (89.0)	0.015 (0.001–0.030)	(Reference)	–
Minor complication	16 (11.0)	-0.013 (-0.067–0.419)	-0.028 (-0.075–0.019)	0.240
No major complications	121 (83.4)	0.020 (0.004–0.037)	(reference)	–
Major complication	24 (16.6)	-0.029 (-0.061–0.004)	-0.049 (-0.088 to -0.010)	0.014
No infection	131 (90.3)	0.016 (0.001–0.032)	(Reference)	–
Infection	14 (9.7)	-0.028 (-0.069–0.012)	-0.045 (-0.094–0.005)	0.076
No cardiovascular complications	126 (86.9)	0.015 (-0.001–0.031)	(Reference)	–
Cardiovascular complication	19 (13.2)	-0.007 (-0.049–0.036)	-0.022 (-0.066–0.022)	0.327
No other complications	135 (93.1)	0.016 (0.001–0.032)	(Reference)	–
Other complication	10 (6.9)	-0.042 (-0.096–0.012)	-0.059 (-0.116 to -0.001)	0.047
Number of comorbidities				
0	10 (6.9)	0.026 (-0.103–0.158)	(Reference)	–
1	29 (20.0)	0.022 (-0.199–0.145)	-0.004 (-0.069–0.061)	0.906
2	44 (30.3)	0.029 (-0.151–0.175)	0.003 (-0.059–0.065)	0.916
3	24 (16.6)	0.016 (-0.138–0.230)	-0.010 (-0.076–0.057)	0.774
4	22 (15.2)	-0.024 (-0.153–0.165)	-0.050 (-0.117–0.017)	0.143
≥5	16 (11.0)	-0.013 (-0.173–0.182)	-0.039 (-0.110–0.032)	0.277
No significant comorbidities	99 (68.3)	0.030 (0.014–0.046)	(Reference)	–
Significant comorbidities	46 (31.7)	-0.025 (-0.173–0.182)	-0.055 (-0.085 to -0.024)	<0.001

[†]Ordinary least square univariate regression models produced for significance test of differences.

CABG: Coronary artery bypass grafting; PCI: Percutaneous coronary intervention.

Financial & competing interests disclosure

J Martikainen is a partner of ESIOR Oy, which carries out health economic and outcome research studies for pharmaceutical, medical device and food companies. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

Standard protocol approvals, registrations and patient consents. The study was approved by the ethics committee of the hospital. All data used in the study were obtained by routine data collection of the hospital and the patients were not approached in any way because of the study. As all information was collected as a part of routine treatment, informed consent was not required by the ethics committee. The study complies with the Declaration of Helsinki.

Summary points

- Identification of adverse events and learning from them, is essential for improving the quality of healthcare.
- Current approaches have drawbacks as the voluntary reporting systems underestimate the real number of adverse events and reviewing patient records is tedious, time consuming and often not very productive.
- Adverse events usually affect the subjective state of health negatively and are consequently often reflected in poor patient-reported health outcomes.
- Major complications (27 vs 9%, $p = 0.004$) or post-intervention infections (16 vs 5%, $p = 0.031$) were more common among those coronary artery revascularization patients with deteriorated score than patients with improved score.
- Patients with a deteriorated 15D score also tended to have more cardiovascular (19 vs 9%, $p = 0.071$) and minor complications (16 vs 7%, $p = 0.118$).
- Focussing the searching of adverse events to patients with poor patient-reported treatment outcome may help target the search for adverse events to the right patients. This enables more efficient learning from adverse events and consequent improvement of healthcare processes.
- Analysis of patients with a positive or a negative change in health-related quality of life can also improve the selection of patients most likely to benefit from revascularization therapy and, on the other hand, the identification of those that are prone to develop complications and comorbidities and, thus unlikely to gain from revascularization.
- Comparative effectiveness data can play a major role in improving patient safety.

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