TARGETED IDENTIFICATION OF ADVERSE EVENTS IN CORONARY ARTERY DISEASE PATIENTS BASED ON PATIENT-REPORTED OUTCOMES

Running Head: Targeted identification of adverse events in CAD

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Keywords: Cardiology/Cardiovascular, Patient-reported outcomes, Comparative safety

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Structured abstract

Aims: Can focusing the adverse events search to patients with poor patient-reported outcome help in targeting adverse event detection?

Patients&Methods: Coronary artery revascularisation patients of the Kuopio university hospital in 6/2012-8/2104 categorized to 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.

Keywords: Cardiology/Cardiovascular, Patient-reported outcomes, Comparative safety

Introduction

To be able to continuously improve health care, 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 Health Care Improvement (www.ihi.org) has developed the Global Trigger Tool (GTT) which is currently considered as the golden standard for detecting adverse events in patient safety research [3-6]. GTT aims to narrow down, by identifying certain keywords associated with safety incidents, the number of full patient records that need to be reviewed [7].

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 possible to easily identify also 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 and setting

Our hospital has collected HRQoL data with the15D instrument [8-10] 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, CABG, or percutaneous coronary intervention, PCI). 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 [8-10]. The minimal important difference (MID) in the 15D score has been reported to be ±0.015 [11].

Patients having returned both the baseline and the 12-month questionnaires were categorised, 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) (11). 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 rehospitalisation, 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 categorised 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 non-significant (hypertension, uncomplicated diabetes etc.) (Table 1).

As our university hospital serves as a tertiary care centre 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 (95% CI). 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

STATA12.0 (Stata Corp LP, Station, TX, USA) or SPSS 19 (IBM SPSS statistics for Windows, Armonk, 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. Eighty-one (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 group with clinically significantly improved 15D score. The patients with a clinically significant positive 15D score change were on average three 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 to 8.6% of those with a positive treatment result (p=0.004) (Figure 1a). The same was true for post-intervention infections (15.6% vs. 4.9%,

respectively, p=0.031) (Figure 1b). Patients with a poor PRO also tended to have more often minor complications (15.6% vs. 7.4%, respectively, p=0.118) (Figure 1a) and cardiovascular complications (18.8% vs. 8.6%, respectively, p=0.071) (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) (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, CI -0.067-0.419) or major adverse events (-0.029, CI -0.061-0.004) (Table 4). Furthermore, in patients with cardiovascular or infectious complications, the mean 15D score change was always negative although the difference, compared to 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, CI -0.173-0.182) compared to 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. 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 (12).

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, 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 randomised controlled trials. Consequently, our results can probably be generalised 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 health care processes. In the future, wider use of HRQoL measurements for the detection adverse events could be a new approach for harm reduction in health care.

Summary points:

1) Identification of adverse events, and learning from them, is essential for improving the quality of health care.
2) 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.
3) Adverse events usually affect the subjective state of health negatively and are consequently often reflected in poor patient-reported health outcomes.
4) 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 revascularisation patients with deteriorated score than patients with improved score.
5) 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).
6) Focussing the searching of adverse events to patients with poor PRO 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.
7) 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.
8) Comparative effectiveness data can play a major role in improving patient safety.

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**** "This article stresses the importance of learning from mistakes but also the lack of consensus concerning the detection of adverse events."**

(3.) Naessens JM, O'Byrne TJ, Johnson MG, Vansuch MB, McGlone CM, Huddleston JM. Measuring hospital adverse events: assessing inter rater reliability and trigger performance of the Global Trigger Tool. *Int J Qual Health Care.* 22(266–274), (2010). DOI:10.1093/intqhc/mzq026

*** "This article brings forth the Global Trigger Tool (GTT) for assessing adverse events and provides information on its reliability."**

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*** "This article discusses the limitations of voluntary reporting systems in reporting adverse events in hospitals."**

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*** "This article were discusses the need to improve adverse event detection in Norwegian hospitals"**

(7.) Thomas EJ, Petersen LA. Measuring errors and adverse events in health care. *J Gen Intern Med.* 18(1), 61-67 (2003). DOI:10.1046/j.1525-1497.2003.20147.x

**** "This article clarified the strengths and weaknesses of assessing adverse events using different sources"**

(11.) Alanne S, Roine RP, Räsänen P, Vainiola T, Sintonen H. Estimating the minimum important change in the 15D scores. *Qual Life Res. 24(3),* 599-606 (2015). DOI:10.1007/s11136-014-0787-4

**** "This article reports the minimal important difference (MID) value for the 15D HRQoL-instrument"**

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 part routine treatment, informed consent was not required by the ethics committee. The study complies with the Declaration of Helsinki.

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

Adverse event type	Clinically significant	Minor
Cardiovascular complication	Reoperation required	Post-operative hematoma in groin
	Extended hospital stay or rehospitalisation	Arrhythmia
	Neurologic complication (stroke)	Post-operative pneumothorax
	Stent thrombosis during follow-up	Post-operative 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	Post-operative ileus
	Post-operative mental confusion	Ileus
	Hip luxation	Rash (Plavix)
	Peroneal paresis	
Comorbidities in the study population		
	Clinically significant comorbidities	**Clinically non-significant comorbidities**
	Neurologic comorbidities with a physical handicap	Hypertension
	Severe heart condition/ heart failure	Uncomplicated diabetes

Severe lung condition	
Claudication	Asthma
Spinal stenosis	Cancer having been treated earlier
Chronic obstructive pulmonary disease	Tinnitus
Spinal disc herniation during follow up	Benign musculoskeletal disorders
New cancer during follow-up	Benign prostatic hyperplasia
Continuous pain	Eye pain
Ulcerative colitis	Collapse
Asbestosis	Rheumatic disorder
Stroke or other cerebrovascular incident	Pneumonia
Recurrent pneumonia	Parkinson’s disease
Complicated diabetes	Metabolic syndrome
Symptomatic lower limb atherosclerosis	Need for pacemaker during follow-up
	Chronic atrial fibrillation

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

	n (%)	Mean 15D score change (95%CI)	Least Square Difference (95%CI)	P*
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-(-0.015))	<0.001
age under 60	*89 (23.5)*	*0.027 (0.010-0.044)*	*(reference)*	
age 60 to 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-(-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-(-0.066))	-0.075(-0.088-(-0.062))	<0.001

* Statistical significance of difference estimated by Ordinary Least Squares regression.

Table 3 Differences between positive and negative MID size changes in HRQoL

	n (%)	MID n (%)		Unadjusted			Adjusted*		
	N=145 (100.0)	Positive n=81 (55.9)	Negative n=64 (44.1)	OR	95%CI	P**	OR	95%CI	P**
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 n (%)	10 (6.9)	7 (8.6)	3 (4.7)	1.000	(*reference)*		*Omitted due to collinearity****		
1 n (%)	29 (20.0)	19 (23.5)	10 (15.6)	0.814	0.172-3.853	0.796			
2 n (%)	44 (30.3)	30 (37.0)	14 (21.9)	0.918	0.206-4.091	0.911			
3 n (%)	24 (16.6)	11 (13.6)	13 (20.3)	0.363	0.075-1.748	0.206			
4 n (%)	22 (15.2)	7 (8.6)	15 (23.4)	0.200	0.039.1.014	0.052			
≥5 n (%)	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)*				
Operation type 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 and because of collinearity Number of comorbidities were excluded to adjusted logistic regression model

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

		N (%)	Mean 15D change, (95%CI)	Least Square Difference (95%CI)	P*
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 to 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 n (%)		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 n (%)		24 (16.6)	-0.029 (-0.061-0.004)	-0.049 (-0.088-(-0.010))	0.014
No Infection		131 (90.3)	0.016 (0.001-0.032)	reference	
Infection n (%)		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 n (%)		19 (13.2)	-0.007 (-0.049-0.036)	-0.022 (-0.066-0.022)	0.327
No Other complications		135 (93.1)	-0.042 (-0.096-0.012)	reference	
Other complication n (%)		10 (6.9)	-0.042 (-0.096-0.012)	-0.059 (-0.116-(-0.001))	0.047
Number of Comorbidities					
0 n (%)		10 (6.9)	0.026 (-0.103-0.158)	reference	
1 n (%)		29 (20.0)	0.022 (-0.199-0.145)	-0.004 (-0.069-0.061)	0.906
2 n (%)		44 (30.3)	0.029 (-0.151-0.175)	0.003 (-0.059-0.065)	0.916
3 n (%)		24 (16.6)	0.016 (-0.138-0.230)	-0.010 (-0.076-0.057)	0.774
4 n (%)		22 (15.2)	-0.024 (-0.153-0.165)	-0.050 (-0.117-0.017)	0.143

≥5 n (%)	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-(-0.024))	<0.001

*Ordinary Least Square univariate regression models produced for significance test of differences

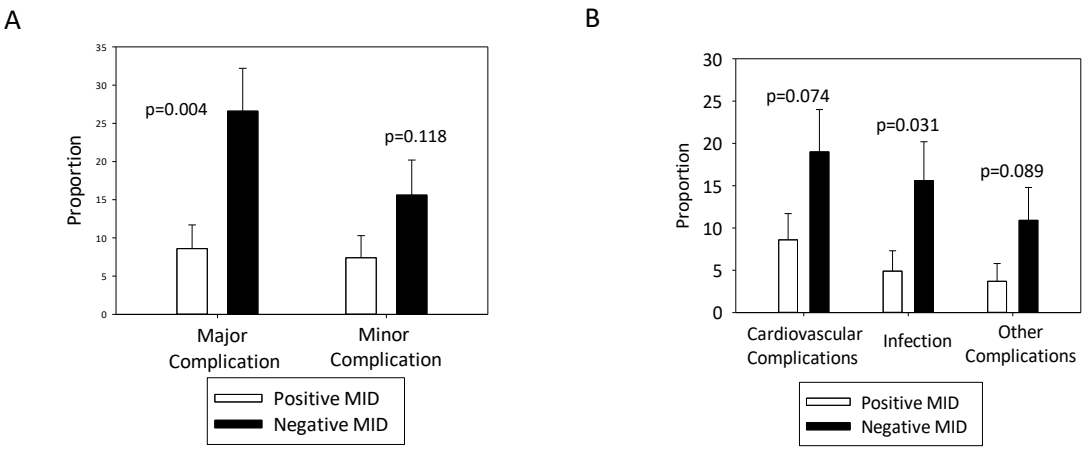

Figure 1a) Major and minor complications and b) cardiovascular complications, infections and other complications among those who experienced a clinically significant improvement (positive minimally important difference; MID) or deterioration in health-related quality of life (negative MID) after coronary artery revascularisation procedure. Significance of differences between positive and negative MID groups were calculated by Ordinary Least Square univariate regressions.