Chapter 5

An evaluation of prognostic factors associated with remission of suicidal ideation in anxious and depressed outpatients: the Leiden Routine Outcome Monitoring study

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Abstract

Suicidal ideation frequently occurs in anxiety and mood disorders. Although in some patients suicidal ideation subsides, in others it persists. Identifying patients at risk of sustained suicidal ideation could aid therapeutic decisions and prevent suicide. Routinely collected data of 777 anxious and/or depressed outpatients with baseline suicidal ideation (measured with Montgomery-Åsberg Depression Rating Scale item 10) and up to 2-years follow-up, were analysed with survival analysis. Low education levels predicted a 14% lower chance of remission of suicidal ideation; a single standard deviation (SD) increase in baseline depression and self-harm scores corresponded to 16% and 23% lower chances of remission. Finally, one SD decrease in general health perception scores corresponded to an 8% reduced chance of remission. Our results underpin the needs of patients with suicidal ideation with low education levels, severe depression, severe self-harm and poor general health perception, who are at increased risk of sustained suicidal ideation.

5.1 Introduction

Among outpatients with mood- and anxiety disorders, thoughts of suicide frequently occur. Prevalences range from 8% in agoraphobia to 84% in major depressive disorder (Eikelenboom et al., 2012). Suicidal ideation (SI) reflects severe suffering, and is a strong predictor of suicide attempts (Ahrens et al., 2000; ten Have et al., 2009) and as such, is targeted in treatment guidelines (Jacobs & Brewer, 2006; van Hemert et al., 2012). Although SI often diminishes during the course of treatment, in a substantial number of subjects it persists over time (Borges et al., 2008), increasing the risk of death by suicide (Hubers et al., submitted for publication). Although numerous studies have focussed on predictors of attempted or completed suicide (Ryan & Large, 2013), relatively little attention has been paid to predicting the course of SI. The identification of patients at risk of sustained SI is urgent, as this could aid clinicians when making therapeutic decisions and, ultimately, prevent suicide.

Previous studies have identified a number of prognostic factors associated with remission of SI: older age, lower education, lower income, cardiovascular disease, trauma, dysthymic disorder, depressive symptoms, anxiety, baseline severity of SI, self-harm, psychotic experiences (hearing sounds or voices that others did not hear), neuroticism, defeat, and externalising behaviour were all associated with lower chances of remission of SI (Enns et al., 2003; Prinstein et al., 2008; Cukrowicz et al., 2009; ten Have et al., 2009; Taylor et al., 2011; Kelleher et al., 2014a). However, previous study populations were diverse (e.g., general population (ten Have et al., 2009; Kelleher et al., 2014a), students (Taylor et al., 2011), adolescent inpatients (Enns et al., 2003; Prinstein et al., 2008), and depressed in- and outpatients (Cukrowicz et al., 2009)), study periods varied from 12 weeks to two years, and the relative prognostic significance of the factors previously identified in different studies remains to be determined, as they were never studied simultaneously. A study focussing on a broad set of previously identified prognostic factors in a naturalistic patient group that often presents with SI will clarify the relative prognostic value of each candidate variable. This will inform clinicians as to what easily obtainable patient characteristics are associated with remission of SI in clinical practice, and help future research aimed at developing a prediction model for remission of SI.

The present study was aimed at evaluating prognostic factors associated with remission of SI over a two-year follow-up period. We analysed data from adult outpatients with SI in a naturalistic treatment setting who were diagnosed with depression and/or anxiety disorder(s). We included a broad set of previously identified prognostic factors: age, education, dysthymic disorder, depression severity, anxiety severity, baseline severity of SI, self-harm, psychotic experiences, neuroticism, and externalising symptoms. In addition to these previously identified prognostic factors, based on clinical experience, we expected that

impulsiveness and subjective general health might also be associated with the course of SI. Both have both been cross-sectionally associated with SI (Goodwin & Olfson, 2002; Brezo et al., 2006). Results of this study will present a synthesis of previous findings. This study is the first to simultaneously evaluate multiple previously identified correlates of the course of SI in a clinical setting. Findings will help clinicians to identify patients at risk of sustained SI, to facilitate treatment decisions, and eventually to prevent suicides.

5.2 Material and methods

5.2.1 Patients and procedure

All subjects were outpatients at Rivierduinen, a mental healthcare provider in the Leiden area in The Netherlands, or at the department of psychiatry of the Leiden University Medical Centre (LUMC). All patients were aged 18 through 65, had adequate command of the Dutch language, and met diagnostic statistical manual of mental disorders- fourth edition-text revision (DSM-IV-TR; American Psychiatric Association, 2000) criteria for one or more of the following disorders: minor or major depressive disorder, dysthymia, panic disorder with or without agoraphobia, agoraphobia without panic, social phobia, generalised anxiety disorder, obsessive compulsive disorder, specific phobia, or post-traumatic stress disorder. In addition, all patients had SI, defined as a score of 2 or higher (Perroud et al., 2009a; Perroud et al., 2009b; van Noorden et al., 2010) on the Montgomery-Åsberg Depression Rating Scale (MADRS; Montgomery & Åsberg, 1979) item 10 on suicidal thoughts (see section 2.2 Measures). All patients were administered self-report and observer-rated measures at intake, and were typically offered repeat questionnaires every 3-4 months of treatment by trained research nurses. This procedure was aimed primarily at informing patients and clinicians and is known as Routine Outcome Monitoring (ROM; De Beurs et al., 2011). Patients who did not have any follow-up assessments or who had missing data (primarily resulting from the failure to administer complete questionnaires) were excluded form analyses. In concordance with Dutch guidelines, all patients received standard outpatient care, which is based on a stepped care model and consists of psychotherapy, pharmacotherapy, or combination therapy (van Fenema et al., 2012). Data were anonymised and their use in scientific research was approved by the Ethical Review Board at the LUMC.

5.2.2 Measures

Primary outcome in this study was SI, which was assessed by a psychiatric research nurse at baseline and follow-up with item 10 of the MADRS (Perroud et al., 2009a; Perroud et al.,

2009b; van Noorden et al., 2010) (figure 1). This item evaluates the presence of suicidal thoughts over the previous week on a seven-point Likert scale by assessing: "Suicidal Thoughts-Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts and the preparations for suicide. Suicide attempts should not in themselves influence the rating"(Åsberg et al., 1978). A score of 0 indicates the patient enjoys life and takes it as it comes; a score of 2 is defined as "weary of life. Fleeting suicidal thoughts," a score of 4 signifies the patient feels he/she is probably better off dead and has suicidal thoughts but no specific plans or intention; and a score of 6 indicates the presence of explicit suicide plans and active preparations. We used a cut-off, with scores of 2 or higher indicating presence of SI and scores below 2 indicating absence or remission of SI (Perroud et al., 2009a; Perroud et al., 2009b; van Noorden et al., 2010). This cut-off has been demonstrated to discriminate well between subjects with and without SI according to a three-questionnaire composite score based on an item response theory graded response model (Perroud et al., 2009b). Age, gender, and education level (low: primary through lower secondary education/ high: higher secondary education through university) were determined at baseline. Baseline DSM-IV-TR diagnostic information was collected using the Dutch version of the MINI International Neuropsychiatric Interview-Plus (MINI-Plus; Sheehan et al., 1998; Van Vliet & De Beurs, 2007). The MINI-Plus has good psychometric properties, with inter-rater reliability between 0.88 and 1.00 and test-retest reliability between 0.76 and 0.93; and adequate validity compared to the Composite International Diagnostic Interview-1 (Lecrubier et al., 1997).

Baseline depression severity was assessed using the MADRS, a 10-item observer-rated scale derived from the abbreviated Comprehensive Psychopathological Rating Scale (CPRS; Åsberg et al., 1978; Goekoop et al., 1992). Items are scored on a 7-point Likert scale (0-6) and the total score is the sum-score of all items. The MADRS has good internal consistency with Cronbach's alpha = 0.86 (Montgomery & Åsberg, 1979). As MADRS item 10 on SI was the primary outcome measure in this study, we calculated an adjusted MADRS score (MADRS-adj), leaving out the suicidal ideation item (item number 10) and summing the remaining 9 items (range 0-54) (Cukrowicz et al., 2009). Anxiety severity at baseline was assessed with the Brief Anxiety Scale (BAS). The BAS is a 10-item observer-rated scale derived from the CPRS. Items cover the main components of all anxiety disorders, including psychological and somatic components, and are scored on a 7-point Likert-scale (0-6), adding up to a total score (range 0-60). Self-harm, psychotic experiences, neuroticism, externalizing behaviour, and impulsiveness were assessed using the Dimensional Assessment of Personality Pathology short form (DAPP-SF; van Kampen et al., 2008), the abbreviated version of the DAPP-BQ (Livesley et al., 1998). Self-harm was measured using the self-harm subscale, psychotic experiences were measured using the cognitive distortion subscale, neuroticism was measured using the affective lability subscale, externalising behaviour was measured using the conduct problems subscale, and

impulsiveness was measured using the stimulus seeking subscale. The DAPP-SF consists of 136 items on a 5-point Likert scale (1-5). Subscales are computed by taking the average of the subscale items (range 1-5). Higher scores are associated with pathology, whereas lower scores indicate normality. The DAPP-SF has good internal consistency with Cronbach's alphas ranging from 0.78-0.89 across subscales (van Kampen et al., 2008). Finally, subjective general health was measured using the general health perception subscale of the Dutch Short Form-36 (SF-36; Ware & Sherbourne, 1992; Aaronson et al., 1998). The SF-36 is a 36-item self-report survey, screening eight domains of general health, suitable for use in diverse populations, including psychiatric patients (McHorney et al., 1994). Measurement scales vary, ranging from yes/no to answers on a 3-, 5- or 6-point scale. Raw scores are linearly converted to 0-100 subscales with higher score representing higher levels of functioning or wellbeing. The SF-36 has good psychometric properties, with Cronbach's alphas between 0.66 and 0.93 (Aaronson et al., 1998).

Figure 5.1 MADRS item 10 on suicidal ideation

10.	***Suicidal Thoughts***
Representing the feeling that life is not worth living, that a natural death would be welcome, suicidal thoughts, and the preparations for suicide. Suicidal attempts should not in themselves influence the rating.	
0	Enjoys life or takes it as it comes.
1	
2	Weary of life. Only fleeting suicidal thoughts.
3	
4	Probably better off dead. Suicidal thoughts are common, and suicide is considered as a possible solution, but without specific plans or intentions.
5	
6	Explicit plans for suicide when there is an opportunity. Active preparations for suicide.

5.2.3 Statistical analyses

Baseline categorical patient characteristics are presented as number (percentage), continuous variables are presented as mean (M) (± standard deviation (SD)) with interquartile range (IQR). Comparisons of demographics between included and excluded patients were made using $\chi 2$ and independent samples t-tests for categorical and continuous variables respectively. Associations between time to remission (MADRS item 10 < 2) and patient characteristics were examined with a Cox proportional hazards model. Cox proportional hazards model is uniquely suited for analysing data of subjects with variable durations of follow-up. As the precise point

in time at which remission was achieved was not known, endpoint was defined as the midpoint between the assessment at which remission was detected and the previous assessment. Maximum follow-up was 24 months. Patients who did not experience an event by that time were censored. The median duration of follow-up was assessed with the reverse Kaplan-Meier method (Schemper & Smith, 1996). The percentage of cumulative remission in the total sample was estimated with the Kaplan-Meier estimator. Hazard Ratios (HR) and their corresponding 95% confidence intervals (CI) were estimated for risks factors associated with time to remission using a Cox model. To facilitate comparability between continuous prognostic factors, z-scores were calculated and used in analyses. To facilitate comparability of HRs, SF-36 general health scores were inverted (i.e. subtracted from 100) so higher scores corresponded to poor subjective general health.

All candidate prognostic variables that achieved significance levels of < 0.10 in univariable analysis were entered in multivariable analysis using a Cox model. Failure to achieve significance ($p \geq 0.05$) in the resulting multivariable model resulted in removal, except for the variables age and gender. Backward stepwise removal of covariates was checked using the p-values of the Wald test and the partial likelihood ratio test, with values ≥ 0.10 demonstrating that removal was justified. To visualise remission over time, 1 minus Kaplan-Meier curves were constructed for all variables in the final model, with separate curves for different levels of categorical variables and tertiles for continuous variables. To explore if the model had predictive value, Harrell's c-statistic was calculated. The c-statistic estimates the probability of concordance between predicted and observed responses (Gonen & Heller, 2005). All tests were two-tailed.

As patients who have recovered from SI could experience relapse (Williams et al., 2006), sensitivity analyses were performed whereby the resulting model was entered on sustained remission. Sustained remission was defined as achieving a score of < 2 on MADRS item 10 without relapsing during the remainder of the follow-up period. In addition, as previous studies varied with regard to follow-up period, we entered the model on remission at six-month- as well as one-year follow-up. Finally, special attention was paid to the potential censoring mechanism in this study. Censoring occurs when a patient has not yet experienced the event of interest by the end of the study. This can occur as a result of loss to follow-up, because a patient experiences a different event that prevents the occurrence of the event of interest (competing risk), or due to administrative censoring (reaching the end of the follow-up period at two years after baseline). A basic assumption in survival analysis is that censoring is non-informative, i.e. the censoring mechanism is independent of the event of interest. In this study, however, one might hypothesize that censoring was not independent of the event being studied (remission of SI): as ROM was periodical and voluntary, it is conceivable that a patient has had a ROM-assessment reflecting persistence of SI, whereupon the patient improved,

completed treatment, and did not return for further assessment. This would mean that achieving remission might have increased patients' chances of being censored. Classical survival techniques cannot be used when the independence assumption between time to event and time to censoring is violated. To further explore this aspect the Inverse Probability Censoring Weighted (IPCW) estimator (Robins & Rotnitzky, 1992; Robins, 1993; Robins & Finkelstein, 2000) was applied to correct for possible informative censoring. More details concerning IPCW and the application to the present data set are described in Willems et al. (Willems et al., submitted for publication). We used R version 3.0.2 (R foundation for Statistical Computing) and SPSS 20.0 (IBM Corp., Armonk, NY, USA) to perform the analysis.

5.3 Results

5.3.1 Sample Characteristics

Between April 2004 and September 2010, a total of 1364 outpatients, diagnosed with DSM-IV-TR mood and/or anxiety disorder(s), expressed suicidal thoughts at intake when presented with MADRS item 10 (score 2 or higher, see figure 1). Of these patients, 575 (42.2%) did not have follow-up ROM assessments. For an additional 12 (0.9%) patients baseline data were missing; consequently, 777 (56.9%) patients were included for analyses. Figure 2 represents a flowchart of inclusion and exclusion. Baseline sample characteristics of the 777 patients in our sample are shown in table 5.1. DSM-IV-TR minor or major depressive disorder occurred in 671 (86.4%) patients, 31 (4.0%) patients suffered from dysthymia. Anxiety disorders occurred in 400 patients, 281 of them had a single anxiety disorder, and 119 patients had multiple anxiety disorders. Anxiety disorders were distributed as follows: 93 (12.0%) patients met diagnostic criteria for panic disorder with or without agoraphobia, 77 (10.0%) patients were diagnosed with agoraphobia without panic, 104 (13.4%) patients had social phobia, 67 (8.6%) patients had generalised anxiety disorder, 62 (8.0%) patients had obsessive compulsive disorder, 11 (1.4%) patients had specific phobia, and post-traumatic stress disorder occurred in 130 (16.7%) patients. Alcohol abuse or dependence occurred in 58 (7.5%) patients, whereas substance abuse or dependence was present in 40 (5.1%) patients. In total, 377 (48.5%) patients met DSM-IV-TR diagnostic criteria for depressive disorder without anxiety disorder, 75 (9.7%) patients met DSM-IV-TR diagnostic criteria for anxiety disorder without depressive disorder, and 325 (41.8%) patients met DSM-IV-TR diagnostic criteria for combined depressive and anxiety disorder.

No significant differences existed between the 777 patients who were included and the 587 excluded patients with regard to gender, education level, diagnosis of dysthymic disorder, depression severity, anxiety severity, baseline SI severity, DAPP-SF cognitive

distortion, and general health perception. Inclusion was associated with age, with patients in the included group being older than those in the excluded group (M = 39.1; SD = 11.8 versus M = 37.1; SD = 12.6; t(1218.41) = -3.004, p = .003), Cohen's d = -0.172. DAPP-SF stimulus seeking scores were lower in the included group (M = 2.25; SD = 0.82 versus M = 2.38; SD = 0.88; t(1358) = 2.728; p = .006), Cohen's d = 0.148. And DAPP-SF behavioural problems scores were lower in the included group (M = 1.52; SD = 0.63 versus M = 1.67; SD = 0.74; t(1134.53) = 3.753; p < .001), Cohen's d = 0.223.

5.3.2 Univariable prognostic factors associated with remission

The median duration of follow-up was 520 days (95% CI = 369 - 671). The cumulative proportion of patients achieving remission of SI during the two-year follow-up period was 76.4% (n = 594), while at two-year follow-up, 40 patients still had SI and continued treatment. The following characteristics were associated with a lower chance of remission at p < 0.10

Table 5.1 Baseline characteristics in 777 depressed and/or anxious outpatients with suicidal ideation.

Categorical variables	**n**	**%**
Gender		
- male	299	38.5%
- female	478	61.5%
Education-level		
- high	426	54.8%
- low	351	45.2%
Major depressive disorder	671	86.4%
Dysthymic disorder	31	4.0%
Anxiety disorder	400	51.5%
Continuous variables	**Mean (±SD)**	**IQR**
Age	39.1 (11.8)	30.0 - 48.0
Suicidal ideation score (MADRS item 10)	2.6 (0.9)	2.0 - 3.0
Depression severity (adjusted MADRS score)	24.9 (6.7)	20.0 - 29.0
Anxiety severity (BAS score)	17.8 (6.3)	13.0 - 22.0
Self-harm (DAPP-SF)	2.7 (1.0)	1.8 - 3.5
Psychotic experiences (DAPP-SF)	2.7 (1.0)	1.8 - 3.5
Neuroticism (DAPP-SF)	3.5 (0.8)	3.0 - 4.1
Externalizing behaviour (DAPP-SF)	1.5 (0.6)	1.0 - 1.8
Impulsiveness (DAPP-SF)	2.3 (0.8)	1.6 - 2.8
General health perception (SF-36)	44.8 (19.9)	30.0 - 55.0

Categorical variables are presented as n (percentage), continuous variables are presented as mean (± standard deviation (SD)), interquartile range (IQR). The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. The Montgomery Åsberg Depression Rating Scale item 10 was used to asses suicidal ideation. BAS denotes Brief Anxiety Scale; adjusted MADRS, Montgomery Åsberg Depression Rating Scale minus the suicidal ideation item; DAPP-SF, Dimensional Assessment of Personality Pathology- Short Form; SF-36, Short Form-36.

(Table 5.2): female gender, lower education, higher SI score at baseline, higher baseline depression score, higher baseline anxiety severity score, higher self-harm score, more severe psychotic experiences, higher baseline neuroticism score, more severe externalising behaviour, and more negative subjective general health. Age, dysthymic disorder, and impulsiveness were not associated with remission at $p < 0.10$.

5.3.3 Multivariable prognostic factors associated with remission

Table 5.3 shows HRs with 95% CI's and p-values for each variable included in the model. Patients with a low education level had a 14% smaller chance of achieving remission of SI ($p = 0.09$) than patients with a high education level; an increase of one SD in depression score resulted in a 16% decreased chance of remission of SI ($p < 0.001$); a single SD increase in the self-harm score resulted in a 23% smaller chance of remission ($p < 0.001$); a single SD increase on the inverted subjective general health (indicating poorer subjective general health) resulted in an 8% lower chance of remission ($p = 0.04$). Figure 3 shows the 1 minus Kaplan-Meier curves for cumulative remission over the two-year follow-up period for each of these prognostic variables. Although statistically significant in univariable analyses, baseline anxiety scores, baseline SI scores, and scores for psychotic experiences, neuroticism, and externalising behaviour did not show significant association with time to remission in the multivariable model. The c -statistic was equal to 0.57.

5.3.4 Sensitivity analyses

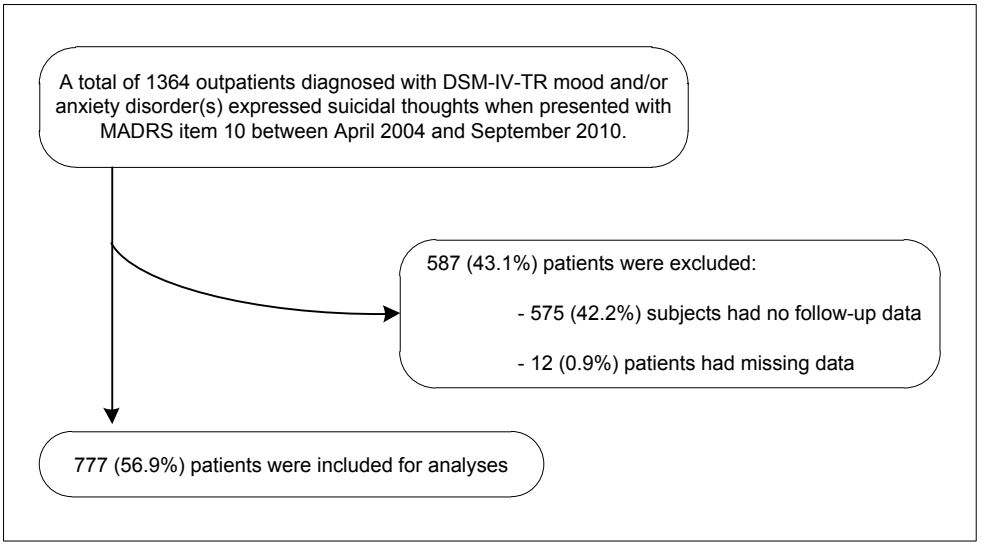
When the model was entered on sustained remission (n = 533); HRs remained comparable to those in the original model (results not shown). Entering the model on remission at six-month as well as one-year follow-up also yielded similar HRs (results not shown). Application of the IPCW method on the data set under study showed no evidence for the presence of dependent censoring. Technical details concerning IPCW method and results for the present dataset are further discussed in Willems et al. (Willems et al., 2016).

Table 5.2 Univariable Hazard Ratios of baseline variables for remission of suicidal ideation in 777 depressed and/or anxious outpatients with suicidal ideation at baseline.

Categorical variables	**HR (95% CI)**	**p-value**
Gender		
- male	1 (ref.)	
- female	0.86 (0.73-1.02)	0.07
Education-level		
- high	1 (ref.)	
- low	0.84 (0.77-0.99)	0.04
Dysthymic disorder		
- no dysthymic disorder	1 (ref.)	
- dysthymic disorder	1.03 (0.68-1.56)	0.89
Continuous variables	**HR (95% CI)**	**p-value**
Age	0.99 (0.91-1.07)	0.75
Suicidal ideation score (MADRS item 10)	0.83 (0.76-0.90)	<.001
Depression severity (adjusted MADRS score)	0.81 (0.75-0.88)	<.001
Anxiety severity (BAS score)	0.90 (0.83-0.98)	0.01
Self-harm (DAPP-SF)	0.75 (0.69-0.81)	<.001
Psychotic experiences (DAPP-SF)	0.89 (0.83-0.97)	.005
Neuroticism (DAPP-SF)	0.93 (0.86-1.00)	0.05
Externalizing behaviour (DAPP-SF)	0.92 (0.84-0.99)	0.04
Impulsiveness (DAPP-SF)	1.01 (0.93-1.09)	0.90
General health perception/ general health perception (SF-36)	0.85 (0.78-0.91)	<.001

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value; ref. signifies the reference category. Remission was defined as a score at follow-up of 1 or less on item 10 of the Montgomery Åsberg Depression Rating Scale. The MINI International Neuropsychiatric Interview-Plus was used to collect diagnostic information. BAS denotes Brief Anxiety Scale; adjusted MADRS, Montgomery Åsberg Depression Rating Scale minus the suicidal ideation item (item 10); DAPP-SF, Dimensional Assessment of Personality Pathology-Short Form; SF-36, Short Form-36. To facilitate comparability of HRs among continuous variables, z-scores were used and SF-36 general health scores were inverted so that higher scores on all measures correspond to greater severity/pathology. HRs <1 indicate lower chances of remission of suicidal ideation whereas HRs >1 indicate better chances of remission of suicidal ideation.

Figure 5.2 Flowchart of inclusion and exclusion in this study



The MINI International Neuropsychiatric Interview was used to collect diagnostic information; DSM-IV-TR denotes diagnostic statistical manual of mental disorders- fourth edition-text revision; MADRS, Montgomery Åsberg depression Rating Scale.

Table 5.3 Multivariable Hazard Ratios of baseline variables for remission of suicidal ideation in 777 depressed and/or anxious outpatients with suicidal ideation at baseline.

	HR (95% CI)	**p-value**
Age	1.02 (0.94 – 1.11)	0.61
Female gender	0.89 (0.75 – 1.06)	0.18
Low education level	0.86 (0.73 – 1.02)	0.09
Depression severity (adjusted MADRS score)	0.84 (0.77 – 0.91)	<.001
Self-harm (DAPP-SF)	0.77 (0.71 – 0.84)	<.001
Subjective general health (general health SF-36)	0.92 (0.85 – 1.00)	0.04

Hazard Ratios (HR) are presented with 95% confidence interval (CI) and p-value; ref. signifies the reference category. Remission was defined as a score at follow-up of 1 or less on item 10 of the Montgomery Åsberg Depression Rating Scale. The MINI International Neuro-psychiatric Interview-Plus was used to collect diagnostic information. Adjusted MADRS denotes Montgomery Åsberg Depression Rating Scale minus the suicidal ideation item (item 10); DAPP-SF, Dimensional Assessment of Personality Pathology- Short Form; SF-36, Short Form-36. To facilitate comparability of HRs among continuous variables, z-scores were used and SF-36 general health scores were inverted so that higher scores on all measures correspond to greater severity/pathology. HRs <1 indicate lower chances of remission of suicidal ideation whereas HRs >1 indicate better chances of remission of suicidal ideation.

5.4 Discussion

This study was aimed at the evaluation of previously identified prognostic factors in the course of SI in a naturalistic sample of outpatients with DSM-IV-TR depression and/or anxiety disorder(s). A longer time to remission of SI over a 2-year follow-up period was associated with a lower level of education, higher depression severity, more severe self-harm, and a poorer subjective general health. Overall, our findings confirm previous reports. An association between sustained or aggravated SI and low education level has previously been found in the general population (ten Have et al., 2009). A low education level is a known risk factor for suicide attempts; possibly through association with lower social economic status (Schmidtke et al., 1996), the same may apply to sustained SI. High baseline depression severity has been identified as a prognostic factor in the course of SI in adolescent (Prinstein et al., 2008) and older (Cukrowicz et al., 2009) patients in previous studies. Present findings indicate that these previous results can be generalised to an adult depressed/anxious outpatient population.

The same goes for the association between self-harm and poorer chances of remission of SI, which was previously reported in adolescent inpatients (Prinstein et al., 2008). Finally, our findings indicate that poor subjective general health was associated with smaller chances of remission. Poor subjective general health has previously been associated with increased risk of SI (Goodwin & Olfson, 2002) but has not been studied in the context of the course of SI. It has been suggested that (feelings of) poor general health could lead to the idea that life is not worth living, or that SI may lead to a negative perception of health (Goodwin & Olfson, 2002), or alternatively, that self-perceived poor health and SI may share an underlying personality construct (Goodwin & Olfson, 2002). However, as our findings reflect associations, causality cannot be attributed.

Previous findings of associations between time to remission and anxiety (ten Have et al., 2009), baseline SI severity (Prinstein et al., 2008), psychotic experiences, and neuroticism (Enns et al., 2003) were confirmed in univariable analyses, but not in the multivariable model, indicating that they did not add explained variance to the variables present in the final model. Higher baseline anxiety severity and higher severity of baseline SI could complicate treatment in general, and thereby predispose patients for poor outcome. Psychotic experiences have been linked to the presence of multiple comorbid Axis I diagnoses (Kelleher et al., 2014b), poorer general and occupational functioning (Kelleher et al., 2014b), neurocognitive deficits (Kelleher et al., 2013a; Barnett et al., 2006), childhood trauma (Kelleher et al., 2013b), and poor coping skills (Lataster et al., 2006; Lin et al., 2011), all of which could be hypothesised to lead to a persistence of SI (Kelleher et al., 2014a). Neuroticism has been suggested to reflect a general tendency to experience negative affect and, as such, contribute to continuation of SI

(Enns et al., 2003). Our findings do however not mean that these factors do not play a role in individual cases.

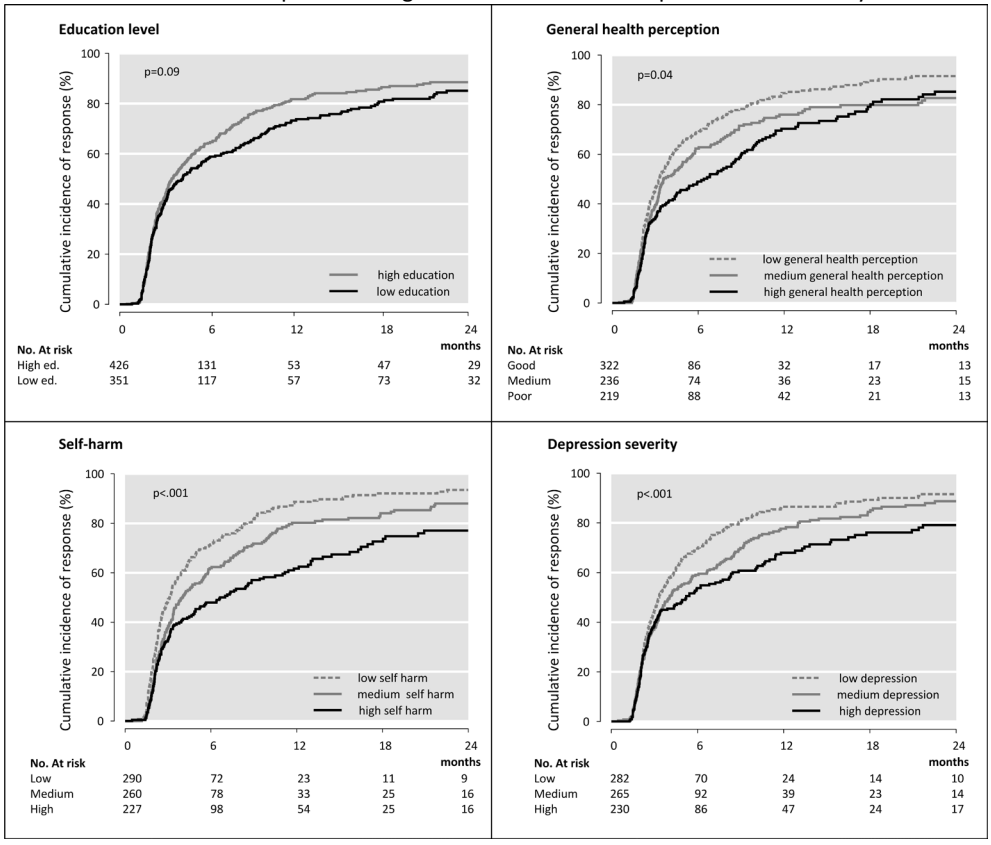
Some previously identified prognostic factors were not associated with the course of SI in our sample. Earlier findings of a predictive value for age (Cukrowicz et al., 2009) were not confirmed. Possibly, the association between age and remission of SI was non-linear and existed exclusively for older (60 years or older) patients in the previous study, but not in our adult (18-65 years) population. A diagnosis of dysthymic disorder was not associated with remission of SI in our sample although this association did emerge in a previous general population study (ten Have et al., 2009). Possibly, this association was specific for general population subjects and did not emerge in our clinical sample, as psychopathology was uniformly present in our sample. Also, it must be noted that dysthymic disorder only occurred in 4% of our sample. Interestingly, we did not confirm reports of an association between high externalising personality traits and better chances of remission of SI (Prinstein et al., 2008), but instead, found that in our sample high externalisation decreased chances of remission. Possibly the association found by Prinstein et al. (Prinstein et al., 2008) is unique to adolescents.

Another possible explanation of the discrepancy between findings may lie in the operationalization of externalisation: Prinstein et al. relied on parent reports of externalising behaviour (Prinstein et al., 2008); we used data from the conduct problems subscale of the DAPP-SF, which measures elements of aggression and rule-breaking embedded in personality. Our finding of poorer chances of remission of SI in those with more externalising behaviour however, is in line with reports of externalising personality traits being associated with increased risk of suicidality (Verona et al., 2004). Also, the hypothesized predictive value of impulsiveness was not found. Finally, although we successfully identified a set of prognostic factors in remission of SI on population level, the c-statistic indicates that our final model has only modest predictive value on individual patient level. Possibly, the exclusive focus on patient characteristics in our study and the previous studies does not provide sufficient information towards prediction, as SI may be associated with contextual factors as well. Further research aimed at prediction of sustained SI may benefit from including contextual factors like life events and social support.

Our study has several strengths: our sample is large and naturalistic, allowing for comorbidity and including not only depressed but also anxious patients. We used a structured clinical diagnostic instrument, computerised data-collection, and data-collection by trained research nurses, all as part of standard care. In addition, we have studied a broad set of potentially relevant patient characteristics, extending upon previous findings, to determine the relative prognostic value of easily obtainable patient characteristics towards remission of SI. However, several limitations exist: First of all, although our data-collection covered a broad range of variables, we were unable to include all previously identified prognostic factors

associated with SI: in our sample no information on childhood trauma (ten Have et al., 2009), cardiovascular disease (ten Have et al., 2009), or level of defeat (Taylor et al., 2011) was available. Second, attrition in our sample was high and the reasons for loss to follow-up (including possible attempted or completed suicide) were unknown. However, attrition is common in observational studies and comparisons between subjects with and without follow-up demonstrated that no important differences existed. Furthermore, application of the IPCW method (Willems et al., submitted for publication) showed no evidence of presence of informative censoring. This indicates that loss to follow-up was not associated with the identified predictors of the course of SI, and as such, findings do not point at completed suicide as a reason for loss to follow-up. Also, we used a single item to assess SI, which may be less suited than a dedicated suicidality questionnaire. It has been demonstrated that different instruments for assessing SI provide diverging estimates of SI prevalence (Vuorilehto et al., 2014). However, a previous study demonstrated that the cut-off < 2 on MADRS item 10 discriminated well between subjects with and without SI, as assessed with a three questionnaire composite score (Perroud et al., 2009b). Furthermore, we have no information on psychiatric history, including previous suicidal behaviour. This information might be relevant and future studies might improve on current findings by including this information. Finally, no information on treatment was available, as such, unfortunately, this could not be included in analyses. However, previous studies in our cohort have demonstrated that treatment was delivered according to guidelines, existing of pharmacotherapy (23%), psychotherapy (59%), or combination therapy (16%) (van Fenema et al., 2012). In spite of these limitations, this study has been the first to simultaneously evaluate previously identified prognostic factors for SI. In addition, we studied these factors in a clinical setting in which SI is highly prevalent. As such, we identified a set of prognostic factors associated independently with remission of SI generalizable to outpatients with depression and/or anxiety disorder(s). Caregivers should be alert to patients presenting with SI who have low education levels, more severe depression, poor subjective general health perception, and who have a history of self-harm.

Figure 5.3 1-minus Kaplan-Meier curves, presenting cumulative incidence of remission of suicidal ideation in 777 outpatients diagnosed ith DSM-IV-TR depressive and anxiety disorders.



1-minus Kaplan-Meier curves are shown for the cumulative incidence of remission of suicidal ideation, defined as a score of 2 or less on item 10 of the Montgomery Åsberg Depression Rating Scale (MADRS) on suicidal ideation. To facilitate presentation, tertiles were constructed for (inverted) general health perception (measured with Short Form-36 subscale general health perception), self-harm (measured with Dimensional Assessment of Personality pathology-Short Form), and depression severity (measured with the MADRS, excluding item 10).

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