Nurse-coordinated care improves the achievement of LDL cholesterol targets through more intensive medication titration

Marjolein Snaterse,1 Harald T Jorstad,2 Marlies Heiligenberg,1 Gerben ter Riet,3 S Matthijs Boekholdt,2 Wilma Scholte op Reimer,1,2 Ron J Peters2

ABSTRACT

Background Nurse-coordinated care (NCC) improves the achievement of low-density lipoprotein-cholesterol (LDL-C) targets after an acute coronary syndrome (ACS). We hypothesised that NCC improves achievement of LDL-C targets through more intensive medication titration.

Methods We used data from Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists (RESPONSE), a multicentre randomised trial on the efficacy of NCC in 754 ACS patients. Follow-up data were collected at 6 and 12 months. To enable comparison between the various types and dosages of statins, we used the average lipid-lowering potency (ALLP, % LDL-C lowering) as an indicator of lipid-lowering medication intensity.

Results Most patients in NCC intervention and usual care groups (96%) had started lipid-lowering therapy during the index hospitalisation. At 6 months, titration activities (up or down) were applied in 45% of NCC patients compared with 24% of patients receiving usual care (p<0.001), and a difference was also seen at 12 months follow-up (62% vs 34%, p<0.001). In patients not on LDL-C target at baseline, titration activities at 6 months were recorded in 63% and 30% of NCC and usual care patients respectively (p<0.001), with increased titration activities in both groups at 12 months (69% vs 43%, p<0.001).

Conclusion NCC is associated with more frequent and intense lipid-lowering medication titration to reach LDL-C targets as compared with usual care alone. Further, merely starting the guideline-recommended dose is insufficient to reach the guideline-recommended LDL-C target level. Nurse-coordinated care, combined with guideline-based titration recommendations, improves ACS patient outcomes.

INTRODUCTION

Among patients with coronary heart disease (CHD), treatment of risk factors is the cornerstone of secondary prevention.1 In the last decade, a substantial increase in antihypertensive and lipid-lowering medication prescriptions has been observed.2 Despite a substantial increase in the number of patients receiving guideline-recommended medication, the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) survey showed that up to 3 years after hospitalisation, two-thirds of patients have uncontrolled hypertension, and only half of the patients achieve the guideline-recommended target level for low-density lipoprotein-cholesterol (LDL-C).3 4 It has been hypothesised that factors contributing to this suboptimal risk factor control include prescriptions with inadequate dosage, inadequate up-titration of medication, poor adherence of patients to recommended lifestyle changes, poor medication compliance and low standards of follow-up care.5

Nurse-coordinated care (NCC) has shown to be a promising strategy to improve secondary prevention, and is currently recommended in the 2016 European prevention guidelines.1 In line with this recommendation, we found in a recent systematic review that NCC programmes successfully reduce systolic blood pressure and LDL-C.6 However, a clear understanding of how NCC improves achievement of LDL-C targets is still needed.

What is already known about this subject?
Nurse-coordinated care improves the achievement of low-density lipoprotein-cholesterol (LDL-C) targets after an acute coronary syndrome (ACS).

What does this study add?
Nurse-coordinated care is associated with more frequent and intense lipid-lowering medication titration to reach LDL-C targets as compared with usual care alone.

How might this impact clinical practice?
Merely starting the guideline-recommended dose is insufficient to reach the guideline-recommended LDL-C target level. Nurse-coordinated care, combined with guideline-based titration recommendations, improves ACS patient outcomes.

1ACHIEVE Centre for Applied Research, Faculty of Health, Amsterdam University of Applied Sciences, Amsterdam, Netherlands
2Department of Cardiology, Academic Medical Center, University of Amsterdam, Amsterdam, Netherlands
3Department of General Practice, Academic Medical Center, Amsterdam, Netherlands

Correspondence to
Marjolein Snaterse, m.snaterse@hva.nl, m.snaterse@amc.uva.nl

KEY QUESTIONS

What is already known about this subject?
Nurse-coordinated care improves the achievement of low-density lipoprotein-cholesterol (LDL-C) targets after an acute coronary syndrome (ACS).

What does this study add?
Nurse-coordinated care is associated with more frequent and intense lipid-lowering medication titration to reach LDL-C targets as compared with usual care alone.

How might this impact clinical practice?
Merely starting the guideline-recommended dose is insufficient to reach the guideline-recommended LDL-C target level. Nurse-coordinated care, combined with guideline-based titration recommendations, improves ACS patient outcomes.
the effect of medication titration in NCC, but it has been hypothesised that medication titration could cause this effect.7

To address this gap in knowledge, we investigated the process of medication titration in the treatment of LDL-C in NCC. We used data from the Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists (RESPONSE) trial (see below). As the lifestyle risk factors were comparable in both groups in the study, the previously reported improvement of the proportion of patients on target for LDL-C in the NCC intervention group could not be explained by lifestyle changes. Additionally, participating nurses in this trial reported that the NCC intervention allowed them more frequent contact with patients and the opportunity to monitor targets more carefully.8 We therefore hypothesised that lipid-lowering medication titration activities occurred more often in the NCC than usual care group, and that this led to better achievement of LDL-C targets.

METHODS
Study design and population
We used data from the RESPONSE trial, a multicentre randomised clinical trial including 754 patients from 11 centres in the Netherlands.9 The study was designed to quantify the impact of a practical, hospital-based nurse-coordinated prevention programme on cardiovascular risk in patients discharged after an acute coronary syndrome (ACS), as compared with usual care alone. Patients aged 18–80 years were eligible if they had been diagnosed with ACS within 8 weeks prior to entry into the trial. Patients were excluded if they (1) were unable to visit the nurse-coordinated prevention programme, (2) were not available for follow-up, (3) had a limited life expectancy (<2 years), and (4) were diagnosed with heart failure New York Heart Association class III or class IV.

Nurse-coordinated care
Nurses participating in the NCC programme were registered nurses with at least a 4 years bachelor’s degree in nursing. They had experience in cardiovascular care and were trained in motivational interviewing. Patients in the NCC group visited the outpatient clinic up to four times during the first 6 months after inclusion, in addition to outpatient clinic visits to their cardiologist (usual care). During each nurse visit, cardiovascular risk factors were assessed, lipid profiles (including LDL-C) were reviewed, medication therapy evaluated and patient compliance with medical treatment and lifestyle recommendations was encouraged. To achieve the target lipid levels, the nurses were also encouraged to titrate medication in collaboration with the treating cardiologist.

Data collection
Data on clinical and demographic characteristics and CHD risk factors were collected at baseline and at 6 and 12 months after randomisation. Baseline measurements were performed within 8 weeks after ACS. Patients were enrolled at an average of 4 weeks (SD 2.7) after the ACS. Data on medication use was collected at baseline, 6 months and 12 months follow-up. The data on lipid-lowering medication included number of lipid-lowering medications and, for each medication, the generic name, dosage and frequency. When LDL-C was not on target during the four NCC visits, nurses documented when medication was changed during the NCC visit, and if the treating specialists were consulted and/or patients were referred to treating specialists. All venous blood measurements were taken after a minimum of 8 hours of fasting. The target for LDL-C level was ≤2.5 mmol/L, as recommended by the national CVD prevention guideline at that time.10 Dyslipidaemia was defined by the following criteria: a history of deviated serum cholesterol values (LDL-C >4 mmol/L, HDL-cholesterol <1.0 mmol/L, triglycerides >2 mmol/L or total cholesterol >5 mmol/L) or treatment for dyslipidaemia. Further details on the trial have been published previously.9,11

Lipid-lowering medication intensity and titration
Our main outcome of interest was the proportion of patients with up-titration or down-titration activities in the NCC compared with usual care, assessed by changes in lipid-lowering medication intensity at 6 months and 12 months, relative to baseline medication intensity. The 6 months follow-up visit was performed directly after completion of the NCC intervention (ie, after up to four NCC visits), while between 6 and 12 months follow-up, no specific interventions took place in either group. To account for the use of different lipid-lowering agents and dosages, the intensity of each prescription was expressed as a potential average lipid-lowering potency (ALLP, % LDL-C lowering) ranging from 13 to 70.12 ALLP and up-titration or down-titration was measured at 6 and 12 months follow-up. Up-titration was defined as an increase in ALLP as compared with baseline ALLP, whereas down-titration was defined as a decrease in ALLP.

As the Dutch guideline for cardiovascular risk management recommends starting with simvastatin 40 mg daily when patients are diagnosed with ACS,13 we defined simvastatin 40 mg as the lowest recommended dose approved for the management of ACS.

Statistical analysis
Comparisons between groups were performed using χ² test for categorical variables. Differences between characteristics of up-titrated and down-titrated patients were analysed by the χ² test. The p values presented in figure 1 were up-titration versus no titration (none), and down-titration versus no titration (none). A two-sided p value of <0.05 was considered statistically significant. As ALLP is not a continuous variable, we expressed ALLP as a sum of the prescribed potencies per group. SPSS Statistics for Macintosh, V.22.0. (Armonk, New York, USA) was used for descriptive statistical analyses.
Cardiac risk factors and prevention

In order to include the NCC intervention effect at 6 months, we plotted ALLP changes between baseline and 6 months. We assessed if patients in the NCC group who were (not) on target at baseline received greater intensity changes than those in the usual care group by estimating the interaction between treatment arm and (not) being on target at baseline in a linear regression analysis. These analyses were performed using Stata V.13.1 (College Station, Texas, USA).

To check for selective dropout, we used a logistic regression model and regressed a binary variable indicating missingness (1=yes, 0=no) on the following variables as predictors of missingness under the hypothesis that if all ORs were close to 1, selective dropout due to these predictors is unlikely: age, gender, education level, index event, history of CVD, alcohol, smoking at baseline, diabetes mellitus and their interaction with randomisation group.

RESULTS

Our population consisted of 754 patients with a mean age of 58 years (SD 10.1), 80% were men. The majority (73%) had no history of CVD prior to the index hospitalisation. As previously described, baseline patient characteristics did not differ between the NCC and usual care groups.9 In the NCC group, 92% of 365 patients attended all four NCC consultations as scheduled during the first 6 months. In total, 46 patients in the intervention and 33 patients in the usual care group had one or more missing values for our analyses (11%). Logistic regression did not reveal an indication for selective dropout between the NCC and usual care group.
Titration activity outcome

The proportion of patients with up-titration or down-titration of lipid-lowering medication from baseline to 6 and 12 months follow-up was higher in the NCC group as compared with the usual care group (figure 1). Reflective of the NCC titration intervention, markedly more lipid-lowering titration was seen at 6 months follow-up in the NCC group compared with the usual care group (any titration in all patients 45% vs 24%, p<0.001) (figure 1). At 12 months, a slight increase of titration activities was seen in both groups, yet a statistically significant difference between the two groups remained (52% vs 34%, p<0.001). While both up-titration and down titration in ALLP were seen in both groups, more patients in the NCC than in the usual care group were up-titrated (6 months 30% vs 13%, p<0.001; 12 months 33% vs 19% p<0.001).

In patients not on LDL-C targets at baseline (figure 1), most titration activities (up or down) and the largest difference between NCC and usual care groups were observed in the first 6 months (6 months: 63% vs 30%, p<0.001; 12 months: 69% vs 43%, p<0.001). Similarly, in patients not on target at baseline, also up-titration activities were more often observed in the NCC than in the usual care group, particularly in the first 6 months (6 months: 51% vs 24%, p<0.001; 12 months: 58% vs 33%, p<0.001).

Figure 2 shows all ALLP changes between baseline and 6 months as a function of LDL-C at baseline for NCC and usual care patients (not) on target at baseline. On average, NCC had an (absolute) effect on ALLP compared with usual care alone, especially if patients were not on target at baseline (slope 2.3, (95% CI 0.11 – 4.72)). The differences in SD between NCC and usual care were larger in the NCC group (usual care 4.47 vs NCC 6.71).

**Figure 2** Medication intensity (ALLP) changes between baseline and 6 months, by (not) being low-density lipoprotein-cholesterol (LDL-C) target at baseline for nurse-coordinated care (NCC) (red dots) and usual care (blue dots) patients. Dots represent individual patients. The right lower graph shows, on average, more medication intensity changes in NCC patients not on target at baseline compared with usual care patients (left). The red dashed vertical lines indicate the cut-off LDL-C serum concentration of 2.5 mmol/L. The black lines are the slopes based on a linear regression analysis of the medication intensity changes against LDL-C levels at baseline. ALLP, the average lipid-lowering potency (ALLP, % LDL-C lowering) as an indicator of lipid-lowering medication intensity; LDL, low-density lipoprotein.
care reaffirm the spread of ALLP between these two groups.

**Lipid-lowering medication data**

At baseline, the proportion of patients on lipid-lowering medication was high in both the NCC (96%) and the usual care group (96%), and 68% of all patients were on LDL-C target at baseline (Table 1). Simvastatin (43%), followed by atorvastatin (41%), were the most commonly used lipid-lowering medications prescribed at baseline. During follow-up, a higher proportion of patients in the NCC group were on target compared with the usual care group (6 months: 80% vs 69%, p<0.001; 12 months: 74% vs 64%, p=0.01). Total ALLP was slightly higher in the NCC as compared with usual care at both 6 months (15.003 vs 14.030) and 12 months (14.564 vs 13.964) (Table 1).

**Characteristics of up- titrated and down-titrated patients compared with patients with no titration**

There were no differences in demographic or clinical characteristics as age, gender, level of education, index event or cardiovascular risk factors of up-titrated and down-titrated patients (data not shown). However, up-titrated patients had dyslipidaemia more frequently as compared with patients with no titration (79% vs 70%, respectively, p=0.04), and up-titrations were associated with allocation to the NCC group (62% vs 43%, p<0.001). Down-titrated patients had dyslipidaemia less frequently as compared with patients with no titration (56% vs 70%, respectively, p=0.02). Down-titration was also more frequently seen in patients allocated to the NCC group as compared with patients with no titration (55% vs 43%, respectively, p=0.02).

**DISCUSSION**

Our study demonstrates that NCC in patients with ACS is associated with more frequent lipid-lowering medication titration and with higher ALLP values to reach LDL-C targets as compared with usual care alone. These titrations took place in a relatively short amount of time (four visits in 6 months after an ACS), but changes made in the first 6 months in lipid-lowering medication were also observed 6 months after completion of the NCC programme, and were reflected in a higher proportion of patients reaching targets for LDL-C. Our study took place in a context of high prescription rates of lipid-lowering medication (96% in both groups at baseline). Despite these high prescription rates, the target for LDL-C (2.5 mmol/L) was not reached in a considerable number of patients in both groups (NCC 26% vs usual care 36%). Our study shows that there is considerable room for individual tailoring of lipid-lowering medication therapy, with more both up titration and down titration in medication intensity in the NCC group. While lifestyle modification could account for some changes in LDL-C levels, it is unlikely that this can explain the differences in the higher proportion of patients on target in the NCC group, as lifestyle risk factors were comparable through the study up until 12 months follow-up. Despite a small difference in the total sum of ALLP in both groups at 6 and 12 months, the proportion of individuals on target for LDL-C was markedly higher in the NCC group as compared with the usual care group, reflecting the efficacy of adequate individual medication titration.

Large proportions of high-risk cardiovascular patients have been shown to discontinue their statin therapy, emphasising the need for healthcare providers to discuss medication use with their patients. An integral part of the NCC intervention in our study was interviewing patients about their compliance, asking about barriers...
CONCLUSION

In conclusion, among patients hospitalised for ACS, NCC resulted in more intensive medication titration compared with usual care alone. The greater proportion of patients on LDL-C target at 6 and 12 months follow-up is likely explained by the more intensive titration of lipid-lowering medication in NCC patients compared with usual care alone. Merely starting the guideline-recommended dose is insufficient to reach the guideline-recommended LDL-C target level. NCC, combined with guideline-based titration recommendations, can improve ACS patient outcomes and should become part of routine daily practice.

Contributors MS, HTJ, GIR, SMB, WJMSR and RJG participated in the design of secondary analysis. HTJ was responsible for the coordination and acquisition of the trial data. MS, HTJ and MH attributed to the draft versions of the manuscript. All authors contributed to the preparation, critical review and approved the final manuscript.

Competing interests None declared.

Patient consent Detail has been removed from this case description/these case descriptions to ensure anonymity. The editors and reviewers have seen the detailed information available and are satisfied that the information backs up the case the authors are making.

Ethics approval AMC Amsterdam Medical Ethics committee.

Provenance and peer review Not commissioned; externally peer reviewed.

Open Access This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY 4.0) license, which permits others to distribute, remix, adapt and build upon this work, for commercial use, provided the original work is properly cited. See: http://creativecommons.org/licenses/by/4.0/
REFERENCES

1. Piepoli MF, Hoes AW, Agewall S, et al. 2016 European Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2016;37:2315–81.

2. Kotseva K, De Bacquer D, Jennings C, et al. Time Trends in Lifestyle, Risk Factor Control, and Use of Evidence-Based Medications in Patients With Coronary Heart Disease in Europe: Results From 3 EUROASPIRE Surveys, 1999-2013. *Glob Heart* 2016;2013.

3. Kotseva K, Wood D, De Backer G, et al. EUROASPIRE II: a survey on the lifestyle, risk factors and use of cardioprotective drug therapies in coronary patients from 22 European countries. *Eur J Cardiovasc Prev Rehabil* 2009;16:121–37.

4. Kotseva K, Wood D, De Bacquer D, et al. Cardiovascular prevention guidelines in daily practice: a comparison of EUROASPIRE I, II, and III surveys in eight European countries. *Lancet* 2009;373:929–40.

5. Snaterse M, Dobber J, Jepma P, et al. Effective components of nurse-coordinated care to prevent recurrent coronary events: a systematic review and meta-analysis. *Heart* 2016;102:50–6.

6. van Halewijn G, Deckers J, Tay HY, et al. Lessons from contemporary trials of cardiovascular prevention and rehabilitation: A systematic review and meta-analysis. *Int J Cardiol* 2017;232:294–303.

7. Jørstad HT, Chan YK, Schoot op Reimer WJ, et al. Nurses’ perspectives on nurse-coordinated prevention programmes in secondary prevention of cardiovascular disease: a pilot survey. *Contemp Nurse* 2015;51:96–106.

8. Jørstad HT, van Birgelen C, Alings AM, et al. Effect of a nurse-coordinated prevention programme on cardiovascular risk after an acute coronary syndrome: main results of the RESPONSE randomised trial. *Heart* 2013;99:1421–30.

9. Graham I, Atar D, Borch-Johnsen K, et al. European guidelines on cardiovascular disease prevention in clinical practice: full text. fourth Joint Task Force of the european Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). *Eur J Cardiovasc Prev Rehabil* 2007;14 Suppl 2(Suppl 2):S1–113.

10. Jørstad HT, Alings AM, Liem AH, et al. RESPONSE study: Randomised Evaluation of Secondary Prevention by Outpatient Nurse Specialists: Study design, objectives and expected results. *Neth Heart J* 2009;17:322–8.

11. Besseling J, Kindt I, Hof M, et al. Severe heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis* 2014;233:219–23.

12. NHG Dutch College of General Practitioners. *NHG Dutch guideline cardiovascular risk management*. Utrecht: NHG Dutch College of General Practitioners, 2009.

13. Penning-van Beest FJ, Termorshuizen F, Goetshuis WG, et al. Adherence to evidence-based statin guidelines reduces the risk of hospitalizations for acute myocardial infarction by 40%: a cohort study. *Eur Heart J* 2007;28:154–9.

14. Perk J, De Backer G, Gohlke H, et al. European guidelines on cardiovascular disease prevention in clinical practice (version 2012) : the fifth joint task force of the european society of cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts), *Int J Behav Med* 2012;19:403–88.

15. Shah RJ, McDuffie JR, Hendrix CC, et al. Effects of nurse-managed protocols in the outpatient management of adults with chronic conditions: a systematic review and meta-analysis. *Ann Intern Med* 2014;161:113–21.

16. Voogd-t-Pruis HR, Van Ree JW, Gorgels AP, et al. Adherence to a guideline on cardiovascular prevention: a comparison between general practitioners and practice nurses. *Int J Nurs Stud* 2011;48:798–807.

17. Jiang X, Sit JW, Wong TK. A nurse-led cardiac rehabilitation programme improves health behaviours and cardiac physiological risk parameters: evidence from Chengdu, China. *J Clin Nurs* 2007;16:1886–97.

18. Laurant M, Harmsen M, Wollersheim H, et al. The impact of nonphysician clinicians: do they improve the quality and cost-effectiveness of health care services? *Med Care Res Rev* 2009;66:365–89.

19. Jackevicius CA, Li P, Tu JV, Prevalence TJ. Prevalence, predictors, and outcomes of primary nonadherence after acute myocardial infarction. *Circulation* 2008;117:1028–36.

20. Baigent C, Blackwell L, Emberson J, et al. Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials. *Lancet* 2010;376:179–89.

21. Boekholdt SM, Homingh GK, Mora S, et al. Very low levels of atherogenic lipoproteins and the risk for cardiovascular events: a meta-analysis of statin trials. *J Am Coll Cardiol* 2014;64:485–94.

22. Baigent C, Keech A, Kearney PM, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 23 randomised trials of statins. *Lancet* 2007;366:1267–78.

23. Besseling J, Kindt I, Hof M, et al. Growing heterozygous familial hypercholesterolemia and risk for cardiovascular disease: a study of a cohort of 14,000 mutation carriers. *Atherosclerosis* 2014;233:219–23.