European Journal of General Practice

ISSN: 1381-4788 (Print) 1751-1402 (Online) Journal homepage: informahealthcare.com/journals/igen20

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To cite this article: Clare H Luymes, Wouter de Ruijter, Rosalinde KE Poortvliet, Hein Putter, Huug J van Duijn, Mattijs E Numans, Yvonne M Drewes, Jeanet W Blom & Willem JJ Assendelft (2015) Change in calculated cardiovascular risk due to guideline revision: A cross-sectional study in the Netherlands, European Journal of General Practice, 21:4, 217-223, DOI: 10.3109/13814788.2015.1064389

To link to this article: https://doi.org/10.3109/13814788.2015.1064389

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Published online: 31 Jul 2015.

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European Journal of General Practice, 2015; 21: 217–223

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Original Article

Change in calculated cardiovascular risk due to guideline revision: A cross-sectional study in the Netherlands

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KEY MESSAGE:

- Revising the Dutch guideline on cardiovascular risk management implied a shift in drug recommendation in 12% of the patients.
- GPs should be aware of the possible consequences of guideline revisions for patients.
- Professional medical organizations should develop policies on how to cope with these consequences.

ABSTRACT

Background: Guidelines and accompanying risk charts concerning cardiovascular risk management (CVRM) are regularly revised worldwide.

Objective: To evaluate whether revision of the Dutch CVRM guideline has led to the reclassification of patients and, accordingly, to changes in drug recommendations.

Methods: All medical records (year 2011) of patients aged 40–65 years with no history of cardiovascular disease (CVD) but using antihypertensive and/or lipid-lowering drugs, were selected from the Registration Network of General Practices associated with Leiden University Medical Center. Multiple imputation techniques for missing determinants were used. The individual cardiovascular risk was calculated and the resulting drug recommendation was assessed according to both the 2006 and 2012 versions of the guideline.

Results: In total, 2075 patients were selected, of whom 1248 fulfilled the guideline criteria (systolic blood pressure 115–180 mmHg and total cholesterol/high-density-lipoprotein-cholesterol ratio 3.5–8). According to the 2012 guideline, 58.2% of the patients had low risk and 249 patients (20.0%) shifted to a different risk category. For 150 of these patients (12.0%), this category shift implied a shift in drug recommendation. The probability of shifting in drug recommendation increased with increasing age, cholesterol level, and blood pressure, and by being male.

Conclusion: Guideline revision may have important implications: based on identical values for risk factors, according to the latest revision of the Dutch CVRM guideline 20% of patients shifted in risk category and 12% of the patients shifted in drug recommendation.

Keywords: Cardiovascular diseases, risk assessment, guidelines as topic, preventive medicine, primary prevention

INTRODUCTION

In primary preventive cardiovascular disease (CVD) care, risk classification—based on a patient's absolute risk of developing CVD as calculated by combining several risk factors—is widely used (1–12). Increasing knowledge about the underlying assumptions and calculations of these risk classification systems, and about the effects of interventions, leads to regular revisions of guidelines (1–14).

Like in many other countries, the first Dutch guidelines on the prevention of CVD introduced by the Dutch College of General Practitioners, had a 'single risk factor approach,' i.e. they looked at either blood pressure, or cholesterol levels, or at diabetes as a risk factor, but the

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(Received 16 September 2014; accepted 31 May 2015)

ISSN 1381-4788 print/ISSN 1751-1402 online © 2015 Informa Healthcare
DOI: 10.3109/13814788.2015.1064389

risk factors were not combined into an integrated approach of risk management (15–17). In 2006, the first comprehensive guideline on cardiovascular risk management (CVRM) was introduced (18). Five risk factors for CVD, i.e. age, sex, smoking status, systolic blood pressure (SBP) and total cholesterol/high-density-lipoprotein-cholesterol (TC/HDL) ratio, were integrated into one risk chart depicting absolute cardiovascular risk. This risk chart was based on the SCORE risk function, as described in the European guideline developed by the Third Joint Task Force 2003 (19). A patient's 10-year risk of cardiovascular mortality was calculated, and the need for preventive medication was assessed accordingly, using a 10%, 10-year risk on cardiovascular mortality as threshold for entering the high-risk category.

The latest European guideline on CVD prevention was published in 2012, presenting a risk chart for high CVD risk countries and low CVD risk countries (8). In the Netherlands, a new guideline on CVRM was launched in 2012 as well, presenting a risk chart based on the European risk chart for low CVD risk countries (20). This new guideline included some differences regarding the calculation of CVD risk; differences that are also seen in recent updates of other CVD prevention guidelines (1,2,7,8,11,12). The first difference is that the age range now is set at 40–70 years instead of 40–65 years; second, cardiovascular risk assessment is now based on both cardiovascular mortality and morbidity; third, a 20%, 10–year risk of cardiovascular mortality and morbidity was now chosen as the threshold for entering the high-risk category; and finally, the additional risks by diabetes mellitus and rheumatoid arthritis were quantified into the risk chart.

At first glance, this 2012 guideline identifies more patients requiring preventive medication than the 2006 guideline. However, due to other differences between the two versions (especially the weight of additional risk-increasing factors) the exact implications of the 2012 revision on an individual level are not known.

Although the CVRM guidelines in other countries are also regularly revised and most of them present risk charts (1,2,5–10), to our knowledge the effects of a change of guidelines at the population level have not yet been examined. Therefore, we used data from 19 general practices in the western part of the Netherlands to assess whether patients using preventive cardiovascular medication would shift in risk category according to the most recent revision of the Dutch CVRM guideline, and whether these patients would shift in drug recommendation.

METHODS

Study population

A cross-sectional study was performed with data from the Registration Network of General Practices associated with Leiden University (RNUH—LEO); this is a longitudinal database of electronic medical records (EMRs) of all patients (approximately 30 000) enlisted with 19 regular general practitioners (GPs) (located in four healthcare centres) in the western part of the Netherlands (21).

Medical records of patients aged 40–65 years who were using antihypertensive treatment (anatomical therapeutic chemical codes C02*, C03*, C07*, C08*, C09*) and/or lipid-lowering drugs (C10*) during the whole year 2011 were selected (22). All medical records of patients with previous atherothrombotic CVD (international classification of primary care (ICPC) codes K75, K76*, K89, K90*, K91, K92*, K99*) and not using platelet aggregation inhibitors excluding heparin (anatomical therapeutic chemical code B01AC), providing an undisputed indication for medication, were excluded (23). Medical records of patients with diabetes mellitus (T90*) or rheumatoid arthritis (L88*) were also excluded, as inclusion of medical records of these patients would lead to an overestimation of reclassifications because only the 2012 guideline takes these two diseases into account as quantifiable risk-increasing factors. With these criteria, 2075 medical records of patients were selected.

Classification in risk charts

Based on data in the medical records, we calculated the patient's 10-year cardiovascular risk before start of treatment according to the 2006 and 2012 risk charts respectively, using age, sex, smoking status, pre-treatment SBP and pre-treatment TC/HDL ratio, and assessed the risk category and drug recommendation for each patient according to both guidelines. Pre-treatment values were selected closest to the date the medication was started, up to one year before the start of medication. The same was done for smoking status, except that when the patient was registered as a non-smoker or a former smoker longer than one year ago, we considered the patient a current non-smoker.

To calculate the risk according to both the 2006 and 2012 guidelines, we used the same values of the determinants. Supplementary Appendix 1 to be found online at http://informahealthcare.com/doi/abs/10.3109/13814788.2015.1064389 shows the 2006 risk chart and Supplementary Appendix 2 to be found online at http://informahealthcare.com/doi/abs/10.3109/13814788.2015.1064389 the currently used 2012 risk chart. The Dutch College of General Practitioners provided us with the underlying algorithms of the risk charts of both guidelines. These algorithms were used to calculate cardiovascular risk and are being used by the college itself for their online implementation support; subsequently, patients were divided into the three risk categories (low-, medium- and high-risk) for each of both guidelines.

In both guidelines, drug recommendations depend on a patient's 10-year cardiovascular risk. In low-risk

patients, lifestyle changes are advised and in high-risk patients with hypertension and/or hypercholesterolemia, preventive medication is advised. However, in the medium-risk group, drug recommendations also depend on weighing several additional risk factors, including family history, renal function, overweight and physical activity. Patients in the medium-risk group are regarded either as low-risk patients or as high-risk patients taking into account these additional risk factors and are treated accordingly.

Because the additional risk-increasing factors listed in the 2006 guideline differ from those in the 2012 guideline, we made some assumptions to harmonize these two sets of additional risk factors (Table 1).

When patients were classified in a different risk category according to the 2012 guideline than according to the 2006 guideline, we reported this as a 'shift in risk category'. When the 2012 guideline recommended a different drug treatment for a certain patient than the 2006 guideline, we reported this as a 'shift in drug recommendation'. Thus, patients could shift in risk category but not in drug recommendation (e.g. from low-risk category in 2006 to medium-risk category without additional risk factors in 2012), but also vice versa (e.g. in both guidelines in medium-risk category, but in 2012 requiring a different drug recommendation than in 2006, based on a different weighing of the additional risk factors).

Statistical analysis

Patients' shifts in the risk category and drug recommendation were described using frequency tables. Using an independent *t*-test, mean cardiovascular risk was compared between the group shifting in risk category and the non-shifting group, as well as for the group shifting in drug recommendation versus the group not shifting in drug recommendation. The odds ratios of risk factors for shift in risk category or drug recommendation were calculated with logistic regression analysis to explore further the differences between these groups. We rounded to whole patient numbers in all our analyses.

Missing patient data

Data on SBP were missing in 48.3% of the patients, TC/HDL ratio in 50.2% and smoking status in 48.1%. To deal with missing data, we used multiple imputation techniques generating 10 imputed datasets, all presenting different values of imputed variables because of the between-imputation component of variability (24). The imputation model included the following variables: sex, age, smoking status, SBP, TC/HDL ratio, low density lipoprotein (LDL) cholesterol, antihypertensive medication use, lipid-lowering drug use, family history, exercise, kidney function, and body mass index. The range for imputed values of SBP was set at 50–250 mmHg, and for TC/HDL

Table 1. Differences in additional risk factors, used for determining recommendations for medication in medium-risk patients, between the two Dutch guidelines on cardiovascular risk management (2006 and 2012) and conversion of the determinants registered in the electronic medical record (EMR).

	Additional risk factor		Conversion of EMR registration to be able to assess drug recommendation	
Additional risk factors	2006 guideline	2012 guideline	Registration EMR 2006	Converted to 2012
Family history	CVD in a first-degree relative $<$ 60 years	CVD in a first-degree relative $<$ 65 years	CVD in a first-degree relative $<$ 60 years	Not converted
		CVD in $\geq$ 2 first-degree relatives $<$ 65 years	No CVD in a first-degree relative $<$ 60 years	No CVD in a first-degree relative $<$ 65 years
		CVD in $\geq$ 1 first-degree relatives $<$ 60 years		
Body mass index (BMI)	$>$ 30 kg/m^2	30–35 kg/m^2 $\geq$ 35 kg/m^2	BMI	Not converted
Vascular outcome	Kidney function disorders: eGFR $<$ 60 ml/min/1.73m^2	$<$ 65 years: eGFR $>$ 60 ml/min/1.73m^2 Or $\geq$ 65 years: $>$ 45 ml/min/1.73m^2	MDRD	Not converted
		$<$ 65 years: eGFR 30–60 ml/min/1.73m^2 Or $\geq$ 65 years: 30–45 ml/min/1.73m^2		
	Left ventricle hypertrophy		Not assessed	Not assessed
	Intima thickening carotid artery		Not assessed	Not assessed
	Excessive atherosclerosis		Not assessed	Not assessed
Physical activity		Sedentary lifestyle	Less than ADL	Sedentary lifestyle
		$<$ 30 min/d, $\leq$ 5 d/wk	ADL	Sedentary lifestyle
		$\geq$ 30 min/d, $\geq$ 5 d/wk	More than ADL	$<$ 30 min/d, $\leq$ 5 d/wk
			Healthy	$\geq$ 30 min/ d, $\geq$ 5 d/wk

CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate; MDRD, modification of diet in renal disease; d, day; wk, week; ADL, activities of daily living.

ratio at 1–15 to avoid clinically impossible values. After multiple imputation probabilities of variables, shifts in risk category and drug recommendation were calculated based on the population fulfilling the guideline criteria; as the risk charts use a range for SBP (120–180 mm Hg) and for TC/HDL ratio (4–8), patients with a SBP 115–180 and a TC/HDL ratio 3.5–8 fulfilled guideline criteria, making risk calculation possible. Age, SBP and TC/HDL ratio were quantified using the means and standard deviations; sex and smoking status were quantified as percentages and its ranges.

Sensitivity analysis

Shifts in risk category as described above were compared with the original dataset and with a set with imputed data without range restrictions. All analyses were performed with the IBM SPSS version 20.

RESULTS

Patient characteristics

Mean age of the patients was 55.4 years (SD 3.9), 50.2% were men (range: 49.2–51.2), 16% were smokers (range: 15–18%), mean SBP was 153 mmHg (SD 16.7), and the mean TC/HDL ratio was 5.0 (SD 1.0).

Due to the different values of SBP and TC/HDL ratio in the imputed datasets, the number of patients fulfilling guideline criteria differed per dataset. On average 827 (range: 792–841) out of 2075 patients did not fit the guideline, leading to an eligible study population of on average 1248 patients (range: 1234–1283).

Shifts in risk category and drug recommendation

The percentage of patients remaining in the same risk category was 80% [(999/1248)*100]. Furthermore, 726 patients (58.2% of all patients) had a low risk according to the 2012 guideline despite being treated with preventive medication (Table 2).

In total, 249 patients (20.0%) shifted in risk category due to the new guidelines. In these latter patients, the mean cardiovascular risk according to the 2006 and 2012 guidelines was increased compared with the patients that did not shift in risk category (both $P < 0.0001$). Of those 249 patients, 150 (12.0% of all patients) shifted in drug recommendation. These 150 patients showed a higher cardiovascular risk according to the 2006 and 2012 guideline compared with the group that did not shift in drug recommendation (both $P < 0.0001$). In 126 of these 150 patients (10.1% of all patients) drugs were not recommended according to the 2006 guideline but were recommended according to the 2012 guideline; in the other patients vice versa (Table 2).

Table 2. Patients ($n = 1248$) distributed over the risk categories as well as drug recommendation (yes or no) according to the 2006 and 2012 version of the cardiovascular risk management guidelines (in %[a]).

			2012					
			Low risk		Medium risk		High risk	
		Drug recommendation	Yes	No	Yes	No	Yes	No
2006								
	Low risk	Yes	–	–	–	–	–	–
		No	–	58.2%	7.5%	4.9%	–	–
	Medium risk	Yes	–	0.4%	8.7%	1.3%	4.4%	0.1%
		No	–	0.1%	0.3%	4.6%	2.3%	0.1%
	High risk	Yes	–	–	0.2%	–	7.0%	–
		No	–	–	–	–	–	–

[a]Total percentage is 100.1% due to rounding.

Predictors of shift in drug recommendation

Table 3 shows the differences between the group shifting in drug recommendation and the group not shifting in drug recommendation. Differences were found for age, SBP and TC/HDL ratio: i.e. the higher the age, SBP or the TC/HDL ratio, the greater the probability that a patient would shift in drug recommendation. Moreover, being male also increased the probability of shifting in drug recommendation.

Sensitivity analysis

When we imputed data without range restrictions, there was no difference in the percentage of shifts in risk category compared to the shifts in risk category mentioned above (data not shown). The same results emerged from the complete case analysis ($n = 236$).

DISCUSSION

Main findings

In our primary care cohort, revision of the guideline on cardiovascular risk management led to a shift in risk category in one in five patients (20%) and to a concomitant shift in drug recommendation in 12% of the patients.

In addition, the finding that about 60% of the patients use preventive medication whilst having a low risk suggests considerable overtreatment of low-risk patients.

Strengths and limitations

Data for the present study were based on patients' EMRs because, in the Netherlands, CVRM is predominantly primary care based, and all Dutch citizens are enlisted with a general practice. This ensures that our cohort is a representative sample from the general population that is eligible for primary preventive cardiovascular care. Sampling from a large cohort of patients strengthens the external validity of our results. Moreover, over 96% of

Table 3. Determinants of shift in drug recommendation between the 2006 and 2012 version of the cardiovascular risk management guidelines.

	Shift in drug recommendation			
Determinant	Yes $n = 150$	No $n = 1098$	Odds ratio[a] (95% CI)	P-value
Male			3.521 (1.953–6.329)	< 0.0001
Total *n* (%)	116 (77.0)	511 (46.5)		
Smoker			1.133 (0.564–2.278)	0.719
Total *n* (%)	26 (17.0)	176 (16.0)		
Age (per year)			1.073 (1.032–1.115)	0.001
Mean	57.9	55.0		
Range[b]	41–65	40–65		
SBP (per 10.0 mm Hg)			1.210 (1.047–1.399)	0.011
Mean	157.4	152.1		
Range[b]	115–180	115–180		
TC/HDL ratio (per 1.0)			1.297 (1.064–1.581)	0.011
Mean	5.3	4.9		
Range[b]	3.5–7.9	3.5–8.0		

SBP, systolic blood pressure; TC, total cholesterol; HDL, HDL–cholesterol.
[a]Odds ratios are shown for shift in drug recommendation compared to no shift in drug recommendation.
[b]Lowest and highest value of the separate imputation sets reported as range.

the problems registered in the EMRs of the healthcare centres of RNUH—LEO are coded with an ICPC code (which is higher than in the average Dutch general practices), ensuring a reliable selection of our study participants (25).

We imputed 48.1–50.2% of the SBP, TC/HDL ratio and smoking status-values in the dataset to be able to calculate 10-year cardiovascular risk. This may be a true reflection of the incompleteness of relevant data before deciding on the prescription of preventive medication, but can also be due to the incomplete registration of data in the EMRs. However, the imputed dataset showed the same percentage of shifts in the risk category as the complete case analysis.

Comparison with existing literature

In an earlier study, we found that 61.4% of the patients had a predicted low cardiovascular 10-year risk according to the 2006 Dutch CVRM guideline before start of medication, compared with 70.6% (based on the 2006 version) in the present study (26). Besides this confirmation in a new patient population, the present study reports on the implications of a guideline revision at a population level with regard to shifts in risk categories and drug recommendations.

Scheltens et al., compared the Framingham risk score with the SCORE risk function with regard to the number of patients assigned to treatment; a difference with our study is that we examined an actually revised guideline, making the present study less hypothetical (27). Another additional aspect of this study is that we report the determinants of the patients who shifted in drug recommendation, which can be helpful in daily practice.

In this study, we observed that about 60% of the patients use preventive medication whilst having a low risk. This can be explained by former guidelines (before the guideline on integrated CVRM was issued) recommending preventive medication based on a single risk factor ('hypertension' or 'hypercholesterolemia,' etc.) without taking other risk factors (e.g. age, sex and smoking status) into account and not integrating the risk. It is likely that also a considerable number of low-risk patients in other European countries are unnecessarily treated as well. For example in Germany, as in the Netherlands, the concept of starting treatment based on the total burden of risk was adopted only recently (9,17), although the European guideline adopted this idea much earlier (28).

Implications for research and practice

GPs should be aware that a revised guideline in the area of primary prevention of CVD could have consequences for their patients: it is advisable to re-evaluate drug recommendations in patients assessed according to the former guideline and not yet using preventive treatment.

Then again, a large proportion of patients seem to use medication without a clear indication, irrespective of the version of the guideline used. It remains unclear how to proceed when a revised guideline has a higher threshold for starting preventive medication, resulting in situations where patients may well be advised to stop taking preventive medication they have been using, sometimes for years on a row. Obviously, it is important to establish whether withdrawal of medication in patients with low risk is safe in the long run, and whether this is efficacious and cost effective.

Conclusion

Revision of a guideline in the area of primary prevention of CVD may have a considerable impact on patient care since it may lead to shifts in risk categories and, accordingly, to shifts in drug recommendation. Professional medical organizations in countries with guidelines for primary preventive CVD care, especially when using risk charts, should be aware of these consequences and develop protocols for healthcare professionals on how to cope with these reclassifications.

ACKNOWLEDGEMENTS

Data preparation would not have been possible without help from Margot de Waal and Wendy den Elzen from the Department of Public Health and Primary Care, Leiden University Medical Center, the Netherlands.

Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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Supplementary material available online

Supplementary Appendix Figures 1 and 2.