Adherence by Primary Care Physicians to Guidelines for the Clinical Management of Dyslipidemia

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ABSTRACT: Background: There is a wide treatment gap between evidence-based guidelines and their implementation in primary care. Objective: To evaluate the extent to which physicians "literally" follow guidelines for secondary prevention of dyslipidemia and the extent to which they practice "substitute" therapeutic measures. Methods: We performed a post hoc analysis of data collected in a prospective cluster randomized trial. The participants were 130 primary care physicians treating 7745 patients requiring secondary prevention of dyslipidemia. The outcome measure was physician literal adherence or substitute adherence. We used logistic regressions to evaluate the effect of various clinical situations on literal and substitute adherence. Results: Literal adherence was modest for ordering a lipoprotein profile (35.1%) and for pharmacotherapy initiations (26.0%), but rather poor for drug up-titration (16.1%) and for referrals for specialist consultation (3.8%). In contrast, many physicians opted for substitute adherence for up-titration (75.9%) and referrals for consultation (78.7%). Physicians tended to follow the guidelines literally in simple clinical situations (such as the need for lipid screening) but to use substitute measures in more complex cases (when dose up-titration or metabolic consultation was required). Most substitute actions were less intense than the actions recommended by the guidelines. Conclusions: Physicians often do not blindly follow guidelines, but rather evaluate their adequacy for a particular patient and adjust the treatment according to their assessment. We suggest that clinical management be evaluated in a broader sense than strict guideline adherence, which may underestimate physicians' efforts.

KEY WORDS: adherence, guidelines, atherosclerosis, coronary artery disease, primary care, statins, pharmacotherapy

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The prevention of coronary artery disease remains a major public health challenge [1]. Although evidence-based guidelines [2,3] and effective treatments [4] for dyslipidemia are available, there is still a wide gap between guidelines and practice. The target level of low density lipoprotein cholesterol is not achieved in a large proportion of high risk patients [5]. The treatment gap has been attributed to inadequate adherence to the guidelines (not only as a result of lack of awareness of and familiarity with the guidelines but also because of a lack of agreement on the part of the physician with the guidelines) [6], physician workload, lack of consensus about contraindications, and poor patient adherence [7]. In addition, communication barriers, comorbidities, and psychosocial and socioeconomic factors may affect adherence [8]. The most common shortcoming in lipid management is inadequate screening and monitoring, followed closely by inadequate dose adjustment for patients already being treated for elevated cholesterol [9].

The term "adherence" is used to describe the extent to which physicians follow evidence-based guidelines. Adherence to guidelines is considered an expected practice, and many healthcare organizations measure physicians' performance in terms of adherence to guidelines. Such performance is commonly measured by a binary approach, i.e., a guideline is or is not followed. In many cases, physicians do not adhere strictly to guidelines but tend to tailor diagnostic and therapeutic measures to suit the particular patient. Such "substitute" measures follow the general outline of a guideline but differ from the exact recommendations, e.g., the prescribed dose may be lower or higher than recommended, or the physician may recheck lipid levels instead of initiating statin treatment as recommended. To the best of our knowledge, this phenomenon has not been evaluated previously. This study thus aimed to evaluate the extent to which physicians adhere rigidly to guidelines for secondary prevention of dyslipidemia or whether they practice substitute diagnostic and therapeutic measures.

PATIENTS AND METHODS

We performed a post hoc analysis of data collected in a prospective study, known as the Computerized Community Cardiovascular Control (4C) Intervention, which was aimed to enhance secondary prevention of cardiovascular diseases [10].
The study identified patients requiring modification of lipid management, based on the patients’ lipid profile, medications and clinical background. Each patient was reevaluated every 4 months. Patients were classified into one of the following clinical states, based on timely data that were taken from the patients’ electronic medical records: a) indication for LDL-C screening or monitoring, b) pharmacotherapy initiation with statins for patients with LDL-C > 110 mg/dl or bezafibrates for triglycerides > 200 mg/dl, c) statin dose up-titration or switch to a higher potency statin for patients with LDL-C > 110 mg/dl who were already being treated with a statin, and d) referral for consultation with a metabolic specialist for patients not responding to conventional therapy. The rational clinical states were based on a synthesis of the guidelines of the American College of Cardiology and the American Heart Association (ACC/AHA) [2] and the National Cholesterol Education Program (NCEP-III) [3] with European [11] and Israeli [12] guidelines for dyslipidemia management, modified to the regulations of Clalit Health Services, the largest of the four health insurance funds in Israel.

SUBJECTS AND SAMPLING
The sample included patients aged 20 to 74 years old with diagnoses of clinical atherosclerosis (coronary artery disease, peripheral vascular disease, and/or cerebrovascular accident; International Classification of Diseases codes 410-414, 428, v36.0, v45.81, and v45.82). All patients were members of Clalit Health Services, which serves more than 3.7 million people. The sampling covered only urban clinics, since these clinics treat more than 85% of the patients in the studied geographic region. From a total of 38,612 clinical states identified by the system during the period 1 January 2004 to 15 May 2005, there were 16,287 states (42.1%) in which the patient was considered to have achieved target lipid levels or to have been adequately treated. Eventually the dataset included 22,325 clinical states in 7745 patients sent to 130 physicians in 38 clinics. The protocol was approved by the local institutional ethics review board.

ADHERENCE DEFINITIONS
Physician adherence is commonly evaluated in terms of process measures (e.g., patients receiving treatment) [13], subjective measures (e.g., self-reported adherence) [14], outcome measures (e.g., achieving treatment goals) [9], or treatment given to simulated standardized patients [15]. Here, we define adherence as the response of the physician according to the guidelines within a designated time frame, where the time frame is the usual ‘window of opportunity’ to practice diagnostic and therapeutic actions. We previously used a similar method to explore behavioral responses to clinical reminders [16]. In the current study, we evaluated adherence in two ways – “literal” and “substitute,” meaning, respectively, literally adhering to the guidelines, and practicing different measures than those recommended in the guidelines (e.g., prescribing a medication when lipid screening was recommended). If a physician did not respond with either literal or substitute adherence, we categorized it as non-adherence. Thus, the physician’s response to each clinical state was categorized as literal adherence, substitute adherence, or non-adherence. Prescriptions and referrals for lipid profile and metabolic consultations were extracted from the patients’ electronic medical records.

STATISTICAL ANALYSIS
We tested the literal and substitute adherence in various clinical states. Due to the binary outcome and the hierarchical nature of the data (clinical states clustered in patients, patients clustered in physicians, and physicians clustered in clinics), we specified logistic regression models in the framework of Generalized Estimating Equations [17]. The models included the binomial literal or substitute adherence score as the dependent variable, the current clinical state as a fixed effect, and the clinic, physician, and patient identifiers as random effects for clustering. Each clinical state was analyzed as a case. There was one-to-one assignment of clinical states to patients, patients to physicians, and physicians to clinics. The regressions were run with the SPSS® package version 17.

RESULTS
The clinical characteristics of the 7745 patients are shown in Table 1. For the 22,325 clinical states, there was a need for the following actions to be taken: lipid profile monitoring in

| Table 1. Characteristics of a sample of 7745 patients |
| Age (yrs, mean ± SD) | 62.9 ± 10.0 |
| Gender (% male) | 61.7 |
| Medical history |
| Myocardial infarction | 14.8 |
| Unstable angina | 19.2 |
| Cerebrovascular accident | 23.3 |
| Peripheral vascular disease | 24.5 |
| Percutaneous intervention | 28.9 |
| Coronary bypass surgery | 6.6 |
| Major cardiac event during last year | 34.2 |
| Angina pectoris | 12.2 |
| Risk factors* |
| Dyslipidemia | 77.0 |
| Diabetes mellitus | 35.6 |
| Hypertension | 77.1 |
| Obesity | 25.0 |
| Smoking | 32.3 |
| No. of major risk factors (mean ± SD) | 3.3 ± 1.2 |
| Charlson Comorbidity Index (mean ± SD) | 3.6 ± 2.2 |

* Categories are not mutually exclusive (patients may have more than one diagnosis)

Unless otherwise noted, numbers represent % of patients

LDL-C = low density lipoprotein-cholesterol
In 48.9% of the clinical states in which a referral medication than required (e.g., simvastatin 20 mg instead of 40 mg), the physicians prescribed a medication at a lower dose than required. In 17.2% of the clinical states requiring statin initiation (24.3%) was also taken when lipid screening (30.0%) or pharmacotherapy up-titration (16.1%), and lowest for referrals for metabolic consultations (3.8%). Substitute actions initiations (26.0%) and up-titration, the physicians prescribed a lower dose of medication than required (e.g., simvastatin 20 mg instead of 40 mg). In 48.9% of the clinical states in which a referral for metabolic consultation was required, the physicians prescribed a medication at a lower dose than required.

**Table 2.** Estimated odds ratios of literal and substitute adherence rates and their 95% confidence intervals (n=22,325 clinical states)

<table>
<thead>
<tr>
<th>Clinical state</th>
<th>Beta (SE)</th>
<th>P value</th>
<th>OR (95% CI)</th>
<th>Beta (SE)</th>
<th>P value</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid screening</td>
<td>(Reference category)</td>
<td>1</td>
<td></td>
<td>(Reference category)</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy initiation*</td>
<td>-0.51 (0.05)</td>
<td>&lt; 0.001</td>
<td>0.60 (0.55–0.66)</td>
<td>-0.14 (0.05)</td>
<td>&lt; 0.001</td>
<td>0.87 (0.79–0.95)</td>
</tr>
<tr>
<td>Pharmacotherapy up-titration*</td>
<td>-1.22 (0.05)</td>
<td>&lt; 0.001</td>
<td>0.30 (0.27–0.32)</td>
<td>1.77 (0.04)</td>
<td>&lt; 0.001</td>
<td>5.87 (5.44–6.34)</td>
</tr>
<tr>
<td>Metabolic consultation*</td>
<td>-2.91 (0.17)</td>
<td>&lt; 0.001</td>
<td>0.05 (0.04–0.08)</td>
<td>2.10 (0.07)</td>
<td>&lt; 0.001</td>
<td>8.17 (7.17–9.29)</td>
</tr>
</tbody>
</table>

*Relative to lipid screening The estimated odds ratio (OR) represent the relative odds to adhere to the clinical states (e.g., the odds to literally adhere to pharmacotherapy initiation states are 0.6 times the odds to literally adhere to lipid screening states)

CI = confidence interval

**Table 3.** Segmentation of the literal and substitute responses

<table>
<thead>
<tr>
<th>Clinical state</th>
<th>Lipid profile</th>
<th>Initiation of pharmacotherapy</th>
<th>Lower potency</th>
<th>Pharmacotherapy up-titration</th>
<th>Metabolic consultation</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid profile (n=11,808)</td>
<td>35.1%</td>
<td>21.1%</td>
<td>0.0%</td>
<td>8.5%</td>
<td>0.4%</td>
<td>65.1%</td>
</tr>
<tr>
<td>Pharmacotherapy initiation (n=3313)</td>
<td>17.2%</td>
<td>26.0%</td>
<td>6.0%</td>
<td>1.1%</td>
<td>50.3%</td>
<td></td>
</tr>
<tr>
<td>Pharmacotherapy up-titration (n=5281)</td>
<td>3.1%</td>
<td>70.5%</td>
<td>16.1%</td>
<td>2.2%</td>
<td>92.0%</td>
<td></td>
</tr>
<tr>
<td>Metabolic consultation (n=1923)</td>
<td>0.0%</td>
<td>48.9%</td>
<td>29.8%</td>
<td>3.8%</td>
<td>82.5%</td>
<td></td>
</tr>
</tbody>
</table>

This table enhances data presented in Figure 1. Rows are the possible clinical states, and columns are possible actions taken by the physician. Bold numbers represent literal responses, Roman numbers represent substitute responses. Cells with diagonal lines represent cases with no logical sense (e.g., initiate treatment after a requirement for up-titration, which was triggered only when a treatment had already been initiated). Indeed, in these cases there were actually no responses. The Total column represents the sum of the literal and substitute responses. These numbers correspond with the numbers presented in Figure 1

**ADHERENCE RATES**

Preventive action – literal (26.6% of cases) or substitute (44.2% of cases) – was taken in the 70.8% of the clinical situations in which patients did not meet the guideline goal of LDL-C 100–115 mg/dl. Adherence rates varied among the various clinical state types [Figure 1 and Table 2]. The literal adherence rate was highest for lipid screening (35.1%), lower for pharmacotherapy initiations (26.0%) and up-titrations (16.1%), and lowest for referrals for metabolic consultations (3.8%). Substitute actions were mainly adopted in cases requiring metabolic consultations (78.7%) and pharmacotherapy up-titrations (75.9%) but were also taken when lipid screening (30.0%) or pharmacotherapy initiation (24.3%) was required.

**SEGMENTATION OF SUBSTITUTE ADHERENCE**

Segmentation of the substitute actions showed that physicians mostly chose less intense actions than required [Table 3]: For example, in 17.2% of the clinical states requiring statin initiation, the physicians ordered another lipid profile instead of initiating treatment. In 70.5% of the clinical states requiring statin up-titration, the physicians prescribed a lower dose of medication than required (e.g., simvastatin 20 mg instead of 40 mg). In 48.9% of the clinical states in which a referral for metabolic consultation was required, the physicians prescribed a medication at a lower dose than required.

**DISCUSSION**

Some preventive action (whether literal or substitute) was taken in 70.8% of the clinical states in which patients did meet the guideline goals of LDL-C 100–115 mg/dl. However, literal implementation was performed in only a quarter of the cases and substitute measures were taken in almost half of the cases.
The literal adherence was modest for ordering a lipoprotein profile and pharmacotherapy initiations (~35% and 26%, respectively), but poor for drug up-titrations and referrals for specialist consultation (~16% and ~4%, respectively), with many physicians opting for substitute actions for these clinical states. Physicians tended to follow the guidelines literally in simple clinical states (such as the need for lipid screening) but chose substitute measures in more complex cases (when dose up-titration or metabolic consultation was required). Most substitute actions were less intense than the actions recommended in the guidelines. It should be noted that our analysis pertains only to states in which patients did not meet the target LDL-C level (57.9% of the total cohort) and hence represent the relatively complex patients.

**WHEN PHYSICIANS PRACTICE SUBSTITUTE MEASURES**

Each visit to the physician constitutes an opportunity for initiating preventive actions. We set out to differentiate between actions that adhered literally to the recommended guideline and those for which physicians chose a legitimate substitute measure. Substitute actions might be perceived as deviations from the guidelines, but in real-life clinical practice, guidelines are merely guidelines that cover the majority of patients and may not necessarily be applicable to all patients in all clinical situations [7,18]. In keeping with the opinions of a group of Dutch physicians [19], it is our belief that clinical practice guidelines should complement rather than be a substitute for a physician’s judgment. Thus, we suggest that caution be exercised when referring to adherence as a clear-cut binary response and that physicians not be criticized for making individualized patient decisions [20]. Indeed, the stringent requirement of many health care organizations for physicians to literally comply with guidelines and the use of adherence as a quality performance measure may impose additional pressure on the already busy family physician. Furthermore, taking some action (even a substitute action) can be perceived as being better than doing nothing and should be considered in quality assurance evaluations.

Guideline non-adherence can be rational for a number of reasons, such as lack of patient compliance, short life expectancy, drug contraindication, near-goal lipid levels or other priorities [21], and physician disagreement with the guideline recommendations. Physicians’ beliefs about deviation from guidelines may also be a cause of non-adherence [22]. Moreover, there are often contradictions between the guidelines for dyslipidemia management issued by different organizations, e.g., the American NCEP guidelines, the European prevention guidelines, and the British NICE guidelines [23]. Thus, it is possible that actions taken by a physician according to a particular set of guidelines may be considered as non-adherent according to another set of guidelines. Furthermore, the inability of guidelines to cover all individual patients is recognized as a provider-perceived barrier for guideline adherence [7]. It is also possible that the system’s recommendations were insufficiently accurate. We acknowledge that adherence to guidelines is a controversial subject, with differing opinions about the role of guidelines as strict instructions or as general recommendations. The notion that clinical practice guidelines should complement rather than be a substitute for physician judgment might be one interpretation of our results. Another interpretation might be that further efforts are required to improve physician adherence. However, these two interpretations do not necessarily contradict each other: ideally the physician should follow the guidelines but should adjust them to the specific patient.

**SUBSTITUTE ADHERENCE AND CLINICAL COMPLEXITY**

For our study cohort, the physicians’ actions followed a clear pattern. The literal response to lipid screening states was made in about a third of the cases, while the response to changing the medication plan (initiation or up-titration) was very weak and referrals for metabolic consultation were rare. The substitute responses showed the opposite trend, being evident in cases requiring metabolic consultations and pharmacotherapy up-titrations. Assuming that these cases represent more complex states than those requiring lipid screening or statin initiation, we conclude that the physicians tended to follow the guidelines literally in relatively simple clinical cases but chose substitute measures in more complex cases. Just as the guidelines are less specific for complex cases, the clinical states in such cases are less clinically specific. In addition, complex patients are more likely to have multiple chronic comorbidities, making the prevention of cardiovascular disease merely one aspect of patient care [24]. This consideration may also explain the tendency for implementing substitute measures for complex patients.

**RELUCTANCE FOR TREATMENT INTENSIFICATION**

Dosage titration is not always sufficient to achieve the LDL-C goals, and it is often necessary to switch to a more potent (and often more expensive) statin and/or use combination therapy [25]. Segmentation of the substitute actions shows that the physicians mostly chose less intense actions than required. For example, in 17.2% of the clinical states requiring statin initiation, the physicians chose to refer the patients for another lipid profile test rather than start medication. In 70.5% of the cases requiring statin up-titration and in almost half of the cases requiring specialist consultation, the physicians did indeed prescribe a medication but at a lower dose than required. Caution should be taken when ‘blaming’ the physician for the apparent lack of adherence, since the low rate of intensification may often represent the result of negotiation between the physician and the patient. Thus, a physician might not prescribe a medication when a patient declines to take it.
Patients sometimes refuse drugs because of side effects or other reasons, despite the physician’s recommendation. Thus, low rates of intensification do not necessarily reflect poor quality of care but rather a clinical compromise.

STRENGTH AND LIMITATIONS OF THE STUDY
The strengths of the study are the large size and the nature of the study population – which, being community-based, is thus more representative of real-world practice than populations included in most clinical trials – and the meticulous methodology applied in evaluating outcomes. The fact that the health fund insuring the study population provides all levels of care (primary, secondary, tertiary) to its members promotes data consistency and integrity. It should be remembered, however, that any automated system based on clinical databases might have data flaws, especially when integration between several clinical databases is required. We performed extensive data quality assessments to ensure data quality and completeness. In addition, since this is a real-life population-based study, there are some uncontrolled background factors that can affect adherence, such as patient characteristics, attitudes and beliefs, patient-physician communication, and cultural, socioeconomic and organizational barriers.

CONCLUSIONS
In this study, we introduced a new concept of estimating substitute adherence together with literal adherence. Our analysis showed that in real-life clinical practice, literal adherence with dyslipidemia prevention guidelines was poor. Primary care physicians tended to follow the guidelines literally in simple clinical cases but chose substitute measures in relatively complex cases. We propose that adherence measurement be sensitive to the nature of the ‘tailored’ actions taken by physicians, where the substitute actions may sometimes be more appropriate for a specific patient. Measuring performance merely in terms of strict adherence to a guideline might result in an underestimation of the primary care physician’s efforts. Physicians should thus not be criticized for making individualized patient decisions. It appears that more research is required to understand the underlying reasons for physicians’ non-adherence to guidelines and the clinical effects of substitute adherence.

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References

**Capsule**

**The role of HLA-DR-DQ haplotypes in variable antibody responses to anthrax vaccine adsorbed**

Host genetic variation, particularly within the human leukocyte antigen (HLA) loci, reportedly mediates heterogeneity in immune response to certain vaccines; however, no large study of genetic determinants of anthrax vaccine response has been described. Pajewski et al. searched for associations between the immunoglobulin G antibody to protective antigen (AbPA) response to anthrax vaccine adsorbed (AVA) in humans, and polymorphisms at HLA class I (HLA-A, -B, and -C) and class II (HLA-DRB1, -DQA1, -DQB1, -DPB1) loci. The study included 794 European Americans and 200 African Americans participating in a 43 month, double-blind and placebo-controlled clinical trial of AVA (clinicaltrials.gov identifier NCT00119067). Among European Americans, genes from tightly linked HLA-DRB1, -DQA1, -DQB1 haplotypes displayed significant overall associations with longitudinal variation in AbPA levels at 4, 8, 26 and 30 weeks from baseline in response to vaccination with three or four doses of AVA (global \( P = 6.53 	imes 10^{-4} \)). In particular, carriage of the DRB1-DQA1-DQB1 haplotypes \(^*0101-0102-0602\) (\( P = 1.17 \times 10^{-5}\)), \(^*0101-0101-0501\) (\( P = 0.009\)) and \(^*0102-0101-0501\) (\( P = 0.006\)) was associated with significantly lower AbPA levels. In carriers of two copies of these haplotypes, lower AbPA levels persisted following subsequent vaccinations. No significant associations were observed among African Americans or for any HLA class I allele/haplootype. Further studies will be required to replicate these findings and to explore the role of host genetic variation outside of the HLA region.

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Eliran Israeli

**Capsule**

**Efficacy of a bivalent HPV 16/18 vaccine against anal HPV 16/18 infection among young women**

Anal cancer remains rare (incidence about 1.5/100,000 women yearly), but rates are increasing in many countries. Human papillomavirus (HPV) 16 and 18 infections cause most cases of anal cancer. Kreimer and team assessed the efficacy of an AS04-adjuvanted HPV 16 and HPV 18 vaccine against anogenital infection with HPV 16, HPV 18, or both (HPV 16/18). This randomized double-blind controlled trial, conducted in Costa Rica between 28 June 2004 and 21 December 2005, was designed to assess vaccine efficacy against persistent cervical HPV 16/18 infections and associated precancerous lesions. Eligible women were 18–25 years old, residents of Guanacaste and selected areas of Puntarenas, Costa Rica, in good general health, willing to provide informed consent, and not pregnant or breast-feeding. Participants were randomly assigned (1:1) to receive an HPV vaccine (Cervarix®, GlaxoSmithKline, Rixensart, Belgium) or a control hepatitis A vaccine (modified preparation of Havrix®, GlaxoSmithKline). All women who attended the final blinded study visit and consented to anal specimen collection were included in the analysis (4210 of 6332 eligible women). In the full cohort, vaccine efficacy against prevalent HPV 16/18 infection measured once, 4 years post-vaccination, was lower at the anus (62.0%) compared with the cervix (76.4%). In the restricted cohort, vaccine efficacy against anal HPV 16/18 infection was 83-6%, which was similar to vaccine efficacy against cervical HPV 16/18 infection (87.9%). Safety issues were not addressed in the current analysis. Additional safety data will be published later. The authors conclude that the AS04-adjuvanted vaccine affords strong protection against anal HPV infection, particularly among women more likely to be HPV naive at enrollment.

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“A problem well stated is a problem half solved”

Charles F. Kettering (1876-1958), American inventor and engineer, businessman and the holder of 140 patents