**The attitudes of physicians toward guideline recommendations for the management of dyslipidemia in clinical practice - The VIPFARMA ISCP Project.**

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**Abstract**

Guideline recommendations for the management of dyslipidemia, based on current trial evidence and/or expert consensus, aim at improving atherosclerotic cardiovascular disease progression and clinical outcomes. The degree to which physicians accept and implement these recommendations, however, varies markedly depending on a number of factors.

To explore the different attitudes of physicians regarding international recommendations for the management of dyslipidaemia in routine medical practice, the International Society of Cardiovascular Pharmacotherapy carriedouta survey among physicians taking part in the *Surveillance of Prescription Drugs in the Real World Project (VIPFARMA - ISCP Project)*.

*Methods*. Seven clusters of questions were designed to characterize demographics, institutional profile, medical education, clinical practice profile, knowledge and attitudes regarding the use of statins, PCSK9 inhibitors, and triglyceride lowering agents.

***Results.*** The survey was completed by 898 Argentine physicians, of whom 68.3% were cardiologists and 40.0% had specialties related to cardiovascular prevention. Contrary to the recommendations of the Guidelines, 29.6% of physicians supported LDL goals above 70 mg/dl in secondary prevention. Acceptance of values lower than 70 mg/dl was associated with greater levels of continuing education (OR 0.64, 95% CI 0.45-0.91; p=0.014), specialization in preventive cardiology (OR 0.49, 95% CI 0.28-0.88; p=0.017) or diabetology (OR 0.48, 95% CI 0.24-0.98; p=0.043). A less aggressive attitude toward the achievement of guideline goals, such as rejection of the use of statins in diabetics (OR 2.83, 95% CI 1.30-6.18; p=0.009), reduction in statin dose (OR 2.87, 95% CI 2.02-4.10; p=<0.001) or discontinuation when LDL values less than 35 mg/dl are reached (OR 4.32, 95% CI 1.81-10.29; p=0.001) were observed in physicians who considered LDL values higher than 70 mg/dl as the goal in secondary prevention.

***Conclusions.*** One third of physicians in the survey do not follow goals recommended by international guidelines for secondary prevention. Lower levels of continuing medical education and incomplete knowledge of the recommended treatment goals appear to be important reasons for not implementing guideline recommendations in clinical practice.

**Key words:** Guidelines, clinical practice; dyslipidemia; management statins; continuous medical education

**Background**

Cardiovascular knowledge is rapidly evolving, with new tools becoming available to reduce cardiovascular events and mortality in high-risk populations. Among these tools, drugs for the management of dyslipidemia feature prominently1. Guidelines have continued to propose more ambitious lipid goals due to the emergence of new and powerful therapies that demonstrate better cardiovascular outcomes with a larger LDL-cholesterol reduction 2-6 .

Recommendations based on trial evidence and/or expert consensus, provide physicians clear treatment goals for patients at different levels of cardiovascular risk 7. However an important gap appears to exist between guideline recommendations and “real-world” clinical practice 8-14. Furthermore, international registries such as the European Action on Secondary and Primary Prevention by Intervention to Reduce Events (EUROASPIRE) have demonstrated marked differences in care delivery between guidelines and clinical practice, with a clear geographic variation observed 15.

This study aims to determine whether the attitude of physicians is one of the causes of this discrepancy, which may contribute to many hospitalizations and deaths, with a high cost for health systems 16-17.

The International Society of Cardiovascular Pharmacotherapy (ISCP) designed the *Surveillance of prescription drugs in the real world Project (VIPFARMA - ISCP Project)* as a survey to obtain relevant and representative data from a specific population of physicians regarding adherence to guideline recommended pharmacological therapeutic protocols for the management of dyslipidemia.

**Methods**

This pilot study was conducted in Argentina. A cross-sectional online survey was submitted to physicians of different specialties, mostly cardiology and internal medicine, which frequently treat patients with dyslipidemia. Invitations to participate were sent either directly as personal invitations or as mass invitations through scientific societies. We estimate that the population of physicians who were invited to answer the survey, with management of patients in cardiovascular prevention, was 5000.The questionnaire included 30 questions, using Google Forms (Mountain View, CA). It is found in appendix I.

Questions contained dichotomous, Likert-scale, rank-order, and open-ended response choices. Questions were not compulsory and respondents were allowed to select multiple responses depending on the question content. Questions were divided into seven clusters.

A detailed explanation of the study design, the survey and rationale of each cluster of questions has been previously published 18.

**Statistical analysis**

Continuous variables were expressed as mean and standard deviations or median and interquartile range, according to their distribution. The normality of each variable was evaluated using graphic tools (histograms and normal probability plot) and the Shapiro-Wilk test. Categorical variables were expressed by numbers and percentages.  
Student's test was used for comparisons between groups of the continuous variables that were normally distributed. When the distribution was non-normal, the Wilcoxon rank sum test was applied. Comparisons between proportions were made using the Chi square test or Fisher's exact test depending on the frequency of expected values.  
A multiple logistic regression model was constructed manually to explore which variables were associated with the selection of a LDL cholesterol target in secondary prevention below 100 mg/dl. All variables that obtained a value of p≤0.2 in the univariate model were evaluated in the multiple logistic regression model, as well as those that, due to their clinical relevance, included on a clinical basis. Once the final model was obtained, its predictive capacity was evaluated by constructing a Receiver operating characteristic (ROC) curve, and its goodness of fit was evaluated by means of the Hosmer-Lemeshow test, comparing the predicted values by deciles. In all cases the tests were two-tailed, and an alpha error of 5% was assumed to establish statistical significance. The analyses were performed with STATA version 13.0.

**Results**

The VIPFARMA ISCP Project included 898 surveys answered by physicians. The profile of this population is shown in table 1.

The population was predominantly male (66.1%), cardiologists (68.3%), with more than 10 years of practice (74.3%). They mostly carried out academic activities (80.6%), had access to scientific journals (85.7%) and most of the respondents reported having read at least one scientific article in the last 30 days (88.2%). A significant number of responders reported experience in the management of familial hypercholesterolemia (56.6%) and coronary heart disease.

As shown in table 2, 1/3 of the physicians considered that a target < 100 mg/dl of LDL was a better option than a target of < 70 or < 55 mg/dl in the secondary prevention setting, and one in five used low or moderate statin doses in these patients. In cases where the patient did not reach their LDL goal, one in five physicians reported they would not add another drug. Furthermore, in cases where LDL reduction reached a level of 35 mg/dl, more than 40.0% chose to stop the administration of statins or reduce the dose.

When asked about perceived frequency of side effects that were severe enough to discontinue therapy in high intensity statins, rated on a scale of 1 to 10, 321 surveyed participants (36.1%) answered > 4. When asked to rate the excess risk of developing diabetes in pre-diabetic patients receiving statins, 80.3% of the participants considered it was of no concern, whereas 11.4 % preferred not to use statins in that scenario or considered prediabetes a contraindication to their use.

Controlled trials assessing the efficacy of inhibitors of the proprotein convertase subtilisin–kexin type 9 (iPCSK9) were known by 58.9% of the responders. Regarding the evidence that iPSCK9 could reduce LDL cholesterol by 60% and achieve levels even lower than 40 mg/dl, 69.5% of the participants believed this pharmacological class was beneficial, 26.3% that these drugs should be administered carefully, and 4.3% that they represented a risk. Seven hundred thirty-six participants (82.0%) answered that hypertriglyceridemia contributes to increased cardiovascular risk, 91 (10.1%), believed that it does not, and 62 (7.9%) were uncertain. Finally, 408 responders (45.4%) declared that they usually prescribe omega-3 fatty acids, while 656 (73.1%) prescribe fibrates when plasma triglycerides are over 175 mg/dl.

After adjustment by age, sex, time from completion of medical residency, workplace, inhabitants in city of residence, academic activities, experience in caring for patients with familial hypercholesterolemia, number of medical consultations per week, knowledge of PCSK9 inhibitors, appreciation of the importance of statin adverse effects, opinion regarding the role of triglycerides in cardiovascular risk, and the prescription of fibrates and Omega-3, multivariate analysis showed a inverse association between belief that the LDL cholesterol target in secondary prevention should be >70 mg/dl and the specialty of the medical doctors (preventive cardiology and diabetes) and the performance of academic activities. Otherwise, we found an inverse association between the number of years since graduation and the opinion that use of high intensity statins led to development of diabetes in pre-diabetics (Table 3).

The model showed adequate goodness of fit in the Hosmer-Lemeshow (Table 4) test (p=0.72) and a good predictive capacity assessed with a ROC curve with area under ROC curve = 0.81 (Figure 1).

**Discussion**

This study shows that a significant proportion of physicians have different beliefs regarding the management of dyslipidemia from published guidelines. Indeed the main findings were: a) One in three who look after patients with cardiovascular disease use LDLc goals above those recommended by international guidelines; b) One in five of the physicians surveyed used statins of moderate or low intensity in secondary prevention patients; c) One in five were afraid of the risk of developing new diabetes in prediabetic patients receiving statins; d) One in two of the participants did not know of new drugs such as PCSK9 inhibitors; and e) One in five participants did not consider hypertriglyceridemia as a cardiovascular risk factor, or did not have a formed opinion about it. These findings may partially explain the gap between guidelines and daily clinical practice in the real world, and raises alarm regarding potential impact of the "physicians factor" on patients.

Previously published studies reinforce this perspective. The PALM Registry collected provider surveys for 774 clinicians treating patients at 51 primary care practices, 82 cardiology practices, and 8 endocrinology practices 19. In a hypothetical scenario involving secondary prevention, in patients with persistently high LDL-C despite treatment adherence with high-intensity statin therapy, 26.9% of providers chose to change the statin, 51.4% chose to add a non-statin lipid-lowering agent (ezetimibe, fibrate, fish oil, or bile acid sequestrant), and 18.0% of clinicians chose to not change treatment. These findings are consistent with our study. However, when 288 primary and secondary prevention patients with LDL-C ≥130 mg/dL who were already on high-intensity statin therapy treated by these physicians were evaluated, it was found that in real-life practice these physicians were observed to change the statin in 8 patients (2.8%), add ezetimibe in 11 patients (3.8%), and add fibrate, fish oil, or bile acid sequestrant in 57 patients (20.0%). The majority of patients (n=217, 75.4%) were managed by continuation of statin therapy without change in drug or dose, or addition of a non-statin lipid-lowering medication. Similarly, when only secondary prevention patients were examined (n=161), only 34 (21.1%) were managed with a non-statin lipid lowering medication. In other words, doctors sometimes think one thing but do another. The decision to discontinue statins by physicians is very frequent. The EPHESUS Registry showed that the main causes of discontinuation of statin therapy were negative media coverage (32.1%), and recommendations of physicians to stop the lipid lowering therapy (29.6%) 20. In our study, 40% of physicians agreed to reduce or suspend statins if the LDL values achieved were very low or if the patient was at risk of diabetes. A web-based survey by the European Society of Cardiology and European Atherosclerosis Society was distributed to 70.696 individuals at two time points, before and after publication of the 2019 ESC/EAS dyslipidaemia guidelines 21. Regarding the LDL-C goal (<1.4 mmol/L for very high-risk patients) 31% noted that implementation should consider available local resources and patient preferences. This fact confirms that sometimes doctors make decisions based on their own opinion despite recommendations.

Acknowledging this problem, many institutions have begun to develop a suite of quality indicators to evaluate cardiovascular practice and support the delivery of evidence-based care 22. The Quality Indicator Committee of the European Society of Cardiology (ESC) formed the Working Group for Cardiovascular Disease Prevention Quality Indicators in collaboration with Task Force members of the 2021 ESC Guidelines on Cardiovascular Disease Prevention in Clinical Practice and the European Association of Preventive Cardiology and have selected six domains of care for Atherosclerotic cardiovascular disease (ASCVD) prevention: (a) structural framework, (b) risk assessment, (c) care for people at risk for ASCVD, (d) care for patients with established ASCVD, (e) patient education and experience, and (f) outcomes 23. This initiative has promise to be an effective strategy to bridge the gap between guidelines and clinical practice.

Our study analyzes the attitude of physicians with respect to lipid lowering therapies. We found more agreement with international guidelines in doctors with a preventive specialty and academic activities. Consequently, continuous medical education appears to be as a second tool to reduce the gap.

Important opinion leaders may help motivate physicians to enhance continuous learning. Valentin Fuster described five keys for the success in continuous learning based on a) *Scheduling:*  courses scheduled close to the weekend, so most practitioners are less likely to have to take time off from their regular work b) *Comprehensiveness:* courses that seek to integrate all aspects of the cardiovascular field, specifically, new developments that have transpired over the last year on each subject and expected evolution in the near and distant future c) *Speakers:* colleagues with clinical expertise, who are recognizable and are passionate about the subject matter d) *Presentation length:*  a minimum length of 20 minutes and a maximum of 30 minutes. Lectures that are <20 minutes usually do not fulfill the educational mandate of a comprehensive review, while lectures which surpass 30 minutes tend to lose the attention of the audience. e) *Interactive:* It is important to allow the audience to present questions to the speakers, who are encouraged to answer the questions in ≤1 minute 24.

A decade ago, the results of the PURE study established the need to improve treatment for high-risk patients in middle-income countries such as Argentina 25. The present study helps to characterize knowledge and attitudes of physicians as an important factor in the discrepancies between the recommendations of the guidelines and clinical practice, and may help to find appropriate solutions to these challenges 26.

**Limitations**

Most of the participants in this study were cardiologists, which makes it difficult to extrapolate these findings to other specialties. In addition, most of the participants were professionals linked to scientific societies and with high levels of continuous education. This raises the possibility that prescribing practices in the general medical environment are worse than that found in our survey. The questionnaire used in this study is not validated for this purpose. However, as the recipients were health professionals with a high educational level, it can be speculated that the questions were fully understood, and that there were no misunderstandings in the answers. Finally, it is not possible to establish a linear correlation between the responses to a questionnaire and the behaviors adopted in patient care. Despite this, our study constitutes the first survey on this issue in the region, and we believe that it lays the foundations for developing concrete actions that seek to optimize the management of patients with dyslipidemia.

**Conclusions**

One third of physicians in the survey do not follow goals recommended by international guidelines for secondary prevention. Lower levels of continuing medical education and incomplete knowledge of the recommended treatment goals appear to be important reasons for not implementing guideline recommendations in clinical practice.

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**Legend to the tables and figures**

CENTRAL ILUSTRATION. Main findings of the study. In red, the proportion of physicians who answered according to each sentence.

Table 1. Characteristics of the population surveyed

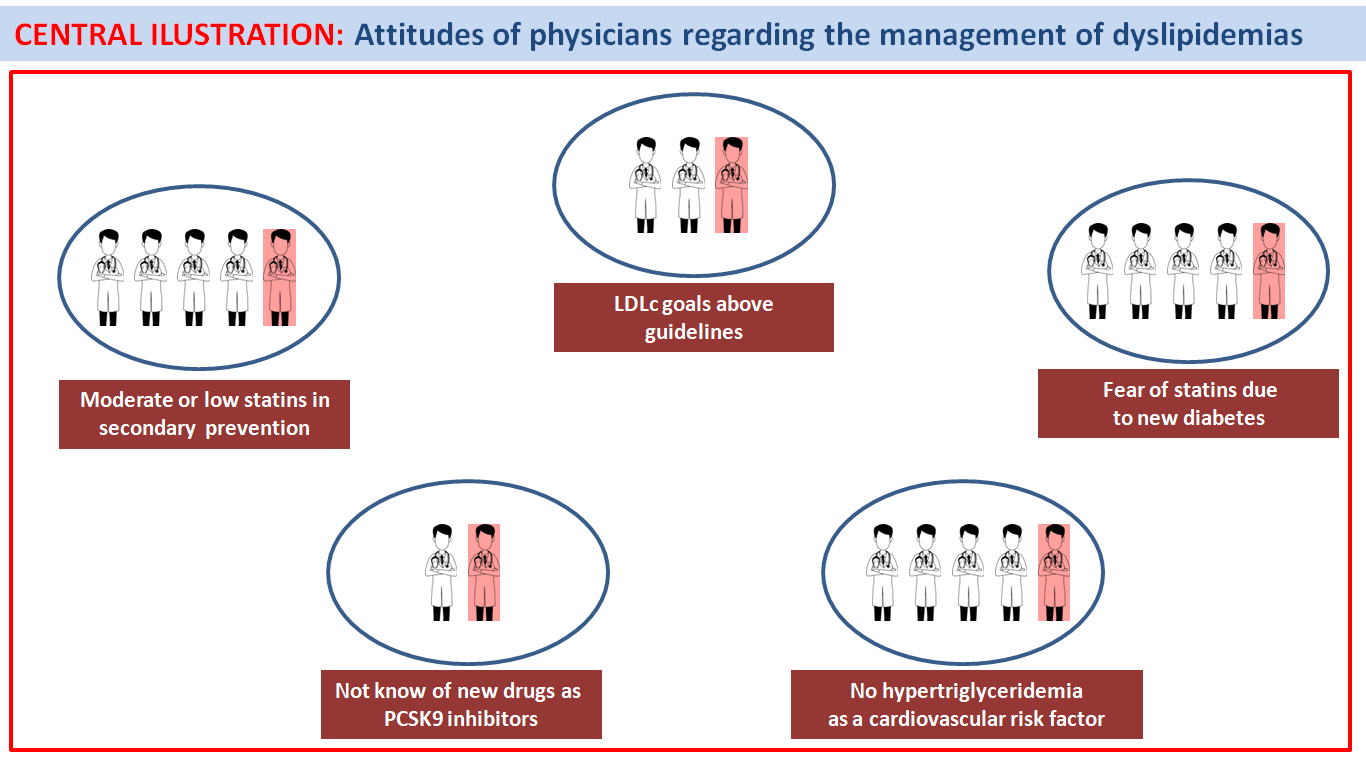
Table 2. Attitudes of responders regarding dyslipidemia goals in secondary prevention and pharmacological management

Table 3. Factors associated with the belief that the target LDL cholesterol in secondary prevention should be > 70 mg / dl

Table 4. Hosmer-Lemeshow test to assess the goodness of fit of the multivariable model.

Figure 1. ROC curve to assess predictive capacity of the multivariable model

**CENTRAL ILUSTRATION**

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**Tables**

**Table1**

|  |  |  |  |
| --- | --- | --- | --- |
| **Profile of the population surveyed** |  | **Number** | **%** |
| Total population |  | 898 | 100% |
| Gender |  |  |  |
|  | Male | 594 | 66.10% |
|  | Female | 304 | 33.90% |
| Specialties |  |  |  |
|  | Cardiology | 513 | 68.30% |
|  | Internal Medicine | 124 | 13.80% |
|  | Primary care | 63 | 7.00% |
|  | Endocrinology | 15 | 1.70% |
|  | Others | 183 | 20.37% |
| Years of practice |  |  |  |
|  | <10 years | 231 | 25.70% |
|  | 10-20 years | 247 | 27.50% |
|  | >20 years | 420 | 46.80% |
| Site of practice |  |  |  |
|  | Private centers | 308 | 34.30% |
|  | Public hospitals | 230 | 27.60% |
|  | Private and public | 155 | 17.30% |
|  | Consulting room | 205 | 21.00% |
| Size of cities (Inhabitants) |  |  |  |
|  | < 100,000 | 193 | 21.50% |
|  | 100,000 to 500,000 | 229 | 25.50% |
|  | >500,000 | 476 | 53.00% |
| Medical education |  |  |  |
|  | Academic activities | 724 | 80.60% |
|  | Access to scientific journal | 770 | 85.70% |
|  | Read an article in the last 30 days | 792 | 88.20% |
|  | None of 3 precedents | 17 | 1.90% |
| Type of patients that follow |  |  |  |
|  | Familial hypercholesterolemia | 508 | 56.60% |
|  | CHD 1-10 patients/week | 438 | 48.80% |
|  | CHD 10-20 patients/week | 275 | 30.60% |
|  | CHD 20-30 patients/week | 103 | 11.50% |
|  | CHD >30 patients/week | 82 | 9.10% |

Table 2

|  |  |  |  |
| --- | --- | --- | --- |
| **Attitudes regarding dyslipidaemia management** |  | **Number** | **%** |
| LDL goal in secondary prevention |  |  |  |
|  | <100 mg/dl | 266 | 29.60% |
|  | <70 mg/dl | 425 | 47.30% |
|  | <55 mg/dl | 196 | 21.80% |
| Statins doses in secondary prevention |  |  |  |
|  | High dose | 732 | 81.50% |
|  | Moderate dose | 80 | 8.90% |
|  | Low dose | 86 | 9.60% |
| In case of not reaching the desired LDL goal |  |  |  |
|  | Add ezetimibe 10 mg/day | 664 | 75.00% |
|  | Wait to next visit | 43 | 4.90% |
|  | Adjust dietary recommendations | 127 | 14.40% |
|  | Add iPCSK9 | 51 | 5.70% |
| In case reach LDL value lower than 35 mg/dl |  |  |  |
|  | Keep the same dose | 522 | 58.10% |
|  | Reduce the dose | 338 | 37.60% |
|  | Stop statin therapy | 38 | 4.30% |
| Statins in pre diabetic patients |  |  |  |
|  | No inconvenience to prescribe | 703 | 79.90% |
|  | Prefer not to use statins | 43 | 4.90% |
|  | This condition is a limitation to use | 62 | 7.00% |
| Regarding the power to reduce LDL with iPCSK9 |  |  |  |
|  | Good expectation about iPCSK9 | 570 | 69.50% |
|  | Should be administered carefully | 214 | 26.10% |
|  | iPCSK9 may involve some risk | 37 | 4.50% |
| Hypertriglyceridemia increase in cardiovascular risk |  |  |  |
|  | Relevant | 736 | 82.00% |
|  | No relevant | 91 | 10.10% |
|  | Not Know | 62 | 7.90% |

Table 3

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Profile of physician responders** |  | **OR** | **IC 95%** | **“p”** |
| > 10 years of practice |  | 1.43 | 1.15 - 1.78 | 0.002 |
| Speciality |  |  |  |  |
|  | Cardiovascular prevention | 0.49 | 0.28 - 0.88 | 0.017 |
|  | Diabetes | 0.48 | 0.24 - 0.98 | 0.043 |
|  | General cardiology | 0.66 | 0.42 - 1.04 | 0.072 |
| Size of the city |  |  |  |  |
|  | 100,000-500,000 inhabitants | 1.74 | 1.12 - 2.69 | 0.014 |
|  | < 100,000 inhabitants | 1.93 | 1.28 - 2.90 | 0.002 |
| All academy activities |  | 0.64 | 0.45 - 0.91 | 0.014 |
| Non use High statins dose |  | 1.33 | 0.86 - 2.06 | 0.205 |
| If control show LDL < 35 mg% |  |  |  |  |
|  | Reduce statin dose | 2.87 | 2.02 - 4.10 | <0.001 |
|  | Stop treatment | 4.32 | 1.81 - 10.29 | 0.001 |
| Knowledge of iPCSK9 main trials |  | 0.42 | 0.29 - 0.61 | <0.001 |
| Attitude when no reach goal of LDL |  |  |  |  |
|  | No change dose and give recommendations | 1.72 | 1.09 - 2.72 | 0.021 |
|  | Wait the next visit to take a decision | 1.91 | 0.92 - 3.93 | 0.081 |
| Those who interpret that AE of statins are frequent (≥4) |  | 1.34 | 0.94 - 1.91 | 0.107 |
| Prescription of statins in prediabetic patients |  |  |  |  |
|  | Use a specific statin | 1.76 | 0.99 - 3.10 | 0.051 |
|  | Use only low dose statins | 1.87 | 0.98 - 3.55 | 0.057 |
|  | Prefer not to use statins | 2.83 | 1.30 - 6.18 | 0.009 |

Table 4

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Group** | **Prob** | **Obs\_1** | **Exp\_1** | **Obs\_0** | **Exp\_0** | **Total** |
| 1 | 0.064 | 2.0 | 4.1 | 85.0 | 82.9 | 87 |
| 2 | 0.088 | 6.0 | 6.4 | 81.0 | 80.6 | 87 |
| 3 | 0.123 | 11.0 | 10.7 | 90.0 | 90.3 | 101 |
| 4 | 0.168 | 12.0 | 10.3 | 60.0 | 61.7 | 72 |
| 5 | 0.219 | 14.0 | 16.4 | 72.0 | 69.6 | 86 |
| 6 | 0.298 | 25.0 | 22.8 | 64.0 | 66.2 | 89 |
| 7 | 0.388 | 26.0 | 29.2 | 59.0 | 55.8 | 85 |
| 8 | 0.530 | 46.0 | 39.4 | 40.0 | 46.6 | 86 |
| 9 | 0.697 | 53.0 | 53.1 | 34.0 | 33.9 | 87 |
| 10 | 0.967 | 66.0 | 68.8 | 20.0 | 17.2 | 86 |

**p-value = 0.72**

Prob= probability; Obs= observed; Exp= expected

Figure 1

