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CLINICAL COMPASS

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JUSTIFICATION FOR THE USE OF STATINS IN PRIMARY PREVENTION: AN INTERVENTION TRIAL EVALUATING ROSUVASTATIN

SUMMARY OF *ROSUVASTATIN TO PREVENT VASCULAR EVENTS IN MEN AND WOMEN WITH ELEVATED C-REACTIVE PROTEIN*

C-reactive protein is an acute phase plasma protein used as a marker for inflammation in infections and arthritis.[1] Levels of high-sensitivity C-reactive protein are used to determine a patient's risk for heart disease and can independently predict future events.[2] Normally, there is no C-reactive protein in the blood and as the level increases, there is a correlated increase in the risk of a cardiovascular event. Patients may have elevated high-sensitivity C-reactive protein without any common risks, such as vascular disease, diabetes, or hyperlipidemia. The rationale for the study is based on the premise that 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors or statins reduce levels of C-reactive protein and may be useful in preventing myocardial infarctions, strokes, and death from cardiovascular causes.[2]

Justification for the Use of Statins in Prevention: an Intervention Trail Evaluating Rosuvastatin (JUPITER) was a randomized, double-blind, placebo-controlled, multicenter trial whose primary objective was to determine if rosuvastatin 20mg decreased the rate of primary cardiovascular events compared to placebo.[2] To be included in the trial participants must have been a male 50 years or older or a female 60 years or older without history of cardiovascular disease and with low-density lipoprotein (LDL) cholesterol less than 130mg/dL, triglyceride level less than 500mg/dL, and high-sensitivity C-reactive protein level greater than or equal to 2mg/L. Additional requirements were written informed consent and willingness to participate, which was tested with a 4-week run in of placebo.

Only patients with good compliance, defined as greater than 80%, during this phase were enrolled in the trial. Exclusion criteria included use of cholesterol lowering medications and/or postmenopausal hormone replacement, hepatic or kidney dysfunction, diabetes, uncontrolled hypertension, uncontrolled hypothyroidism, history of cancer within the past 5 years, history of alcohol or drug abuse, and patients with inflammatory diseases. Participants were randomly assigned in a one to one ratio to receive rosuvastatin 20mg once daily or placebo, and assessments were scheduled at 13 weeks and every 6 months from randomization for 60 months. Each assessment measured compliance, lipid levels, renal and hepatic function, blood glucose and hemoglobin A1C and monitored for outcomes and adverse effects.[2]

The primary endpoint was the occurrence of the first cardiovascular event from the following list: nonfatal myocardial infarction, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, or confirmed death from cardiovascular causes. Secondary endpoints for the study were the individual rates of the components of the primary endpoint. The trial was designed to continue until 520 primary endpoints have been recorded providing the ability to detect a 25% reduction in the rate of primary events. However, findings of an interim efficacy analysis determined that the O'Brien-Fleming stopping boundary had been crossed and the study was discontinued after a median follow-up time of 1.9 years. Analysis was conducted on an intent-to-treat basis. Hazard ratios were calculated based on the Cox proportional-hazards models with 95% confidence intervals. Subgroup analysis was conducted based on predetermined groups.[2]

From the initial screening of 89,890 men and women, 72,088 (80.2%) were deemed ineligible mainly for LDL cholesterol that was too high (N=37,611) and high-sensitivity C-reactive protein levels that were too low (N=25,993). The remaining 19.8% of screened patients underwent a 4 week run-in phase in which 1,521 more participants were dismissed due to poor compliance. The remaining 17,802 participants were randomized equally with 8,901 patients in each study group. Each study population was equally distributed in terms of age, gender, race, body mass index, cholesterol levels, high-sensitivity C-reactive protein levels, and blood glucose level. The study was designed to be diverse in terms of race and gender; women comprised 38.2% of the study population, while Hispanics or Blacks made up 25.2% of the population.[2]

At the time the study was terminated, there were 142 primary endpoints documented in the rosuvastatin group and 251 in the placebo group. The rates of a primary endpoint per 100 person-years were 0.77 and 1.36 in the rosuvastatin and placebo groups, respectively. Rosuvastatin's hazard ratio was 0.56 with a 95% confidence interval ($p<0.00001$; Table 1). The number needed to treat to prevent one primary endpoint is 95 over a 2 year period and 31 over a 4 year period. The results of the secondary endpoints were also significant in preventing the first major cardiovascular event. The results of the primary and secondary endpoints are highlighted in Table 1.[2]

Table 1: Outcomes According to Study Group[2]

End Point	Rosuvastatin (N=8,901)		Placebo (N=8,901)		Hazard Ratio (95% CI)	P Value
	# of pts	Rate per 100 person-yr	# of pts	Rate per 100 person-yr		
Primary end point	142	0.77	251	1.36	0.56 (0.46-0.69)	<0.00001
Nonfatal myocardial infarction	22	0.12	62	0.33	0.35 (0.22-0.58)	<0.00001
Any myocardial infarction	31	0.17	68	0.37	0.46 (0.30-0.70)	0.0002
Nonfatal stroke	30	0.16	58	0.31	0.52 (0.33-0.80)	0.003
Any stroke	33	0.18	64	0.34	0.52 (0.34-0.79)	0.002
Arterial revascularization	71	0.38	131	0.71	0.54 (0.41-0.72)	<0.0001
Hospitalization for unstable angina	16	0.09	27	0.14	0.59 (0.32-1.10)	0.09
Arterial revascularization or hospitalization for unstable angina	76	0.41	143	0.77	0.53 (0.40-0.70)	<0.00001
Myocardial infarction, stroke, or confirmed death from cardiovascular causes	83	0.45	157	0.85	0.53 (0.40-0.69)	<0.00001
Death on known date	190	0.96	235	1.19	0.81 (0.67-0.98)	0.03
Any death	198	1.00	247	1.25	0.80 (0.67-0.97)	0.02

Pts=patients CI=confidence interval

The occurrence of adverse events was similar in the rosuvastatin and placebo groups (1,352 and 1,377, respectively; p=0.60).[2] Myopathy was observed in 10 rosuvastatin patients and 9 placebo patients (p=0.82) and only one case of rhabdomyolysis was reported in the rosuvastatin group. There was a statistically significant number of physician reported newly diagnosed diabetes in the rosuvastatin as compared to the placebo group (270 and 216, respectively; p=0.01). There also was a

statistically significant increase in hemoglobin A1C in the treatment group; however, this is not clinically significant as each study group remained less than 6% as recommended by the American Diabetes Association.[3] See Table 2 for a complete listing of adverse events.[2]

Table 2: Monitored Adverse Events, Measured Laboratory Values, and Other Reported Events of Interests during the Follow-up Period.[2]

Event	Rosuvastatin (N=8,901)	Placebo (N=8,901)	P Value
Monitored Adverse Effects			
Any serious adverse event	1352 (15.2%)	1377 (15.5%)	0.60
Muscular weakness, stiffness, or pain	1421 (16.0%)	1375 (15.4%)	0.34
Myopathy	10 (0.1%)	9 (0.1%)	0.82
Rhabdomyolysis	1 (<0.1%)	0	--
Newly diagnosed cancer	298 (3.4%)	314 (3.5%)	0.51
Death from cancer	35 (0.4%)	58 (0.7%)	0.02
Renal disorder	535 (6.0%)	480 (5.4%)	0.08
Bleeding	258 (2.9%)	275 (3.1%)	0.45
Hepatic disorder	216 (2.4%)	186 (2.1%)	0.13
Laboratory Values			
>100% increase in serum creatinine	16 (0.2%)	10 (0.1%)	0.24
Median glomerular filtration rate at 12 months	66.8	66.6	0.24
ALT >3xULN at consecutive visits	23 (0.3%)	17 (02%)	0.34
Median glycated hemoglobin at 24 months	5.9	5.8	0.001
Other Events			
Newly diagnosed diabetes	270 (3.0%)	216 (2.4%)	0.01
Hemorrhagic stroke	6 (0.1%)	9 (0.1%)	0.44

The trial successfully demonstrated that rosuvastatin significantly reduces the occurrence of cardiovascular events in participants who are at low risk by the current treatment guidelines, but have elevated levels of high-sensitivity C-reactive protein.[2,4] This trial exceeded the expectations of the authors by reducing the hazard ratio by almost twice what was predicted. The therapy used in the trial was considered safe demonstrated by the adverse effect profile being very similar to placebo.[2]

LIMITATIONS

While C-reactive protein is useful as a marker for predicting cardiovascular disease, its role as a diagnostic tool has yet to proven clinically. More studies are needed in order to determine the diagnostic value of C-reactive protein as well as other cardiovascular markers. The study did not include patients with low levels of high-sensitivity C-reactive protein because they felt those patients would be less likely to see a benefit from the therapy. However, these patients would have been useful as a comparative arm in the study.

The trial was stopped early due to the results and their ethical implications; even still longer-term data is needed to ensure safety and efficacy due to that fact that patients in practice will be taking the medication for many years. Based on currently available data, the patients enrolled in this study are at lower risk for events and as such there must be strong justification for recommending long term therapy. More studies with varying doses should be conducted to determine if the therapy decreases the risk enough to warrant nearly life long therapy as some participants in the interquartile had high-sensitivity C-reactive protein levels at 12 months that are categorized as high risk.[1] Also, the long term effects and ramifications of low LDL cholesterol levels must also be investigated. At 12 months, the average level was 55mg/dL and the long term effects of such levels are unknown.

Participants in this trial were screened for compliance, were followed between visits with phone calls, and assessed on their compliance at each assessment. This high level of compliance may not be applicable to the average patient and results may not be duplicated in the practice setting.

Meta-regression analysis was used to determine that the risk reduction seen with rosuvastatin was greater than expected. However, the use of this method has been called into question. This combined with the early termination of the trial may have lead to exaggerated results.[5]

IMPLICATIONS TO CLINICAL GUIDELINES

Current National Cholesterol Education Program guidelines site LDL cholesterol as the primary target for lipid-lowering therapy.[6] A patient's target LDL cholesterol is determined by his/her coronary heart disease (CHD) status and/or CHD equivalents, such as diabetes, atherosclerotic disease, as well as other risk factors such as, age, gender, family history, hypertension, and smoking status.[6] Screening for C-reactive protein is not in the current guidelines as a clear causative link has yet to be confirmed.[1,5] Current guidelines concerning C-reactive protein levels recommend testing patients with intermediate risk if the result of the test would change the course of therapy.[5]

If results from this trial are used to elevate C-reactive protein testing to a more prominent place in practice, there may be an increase in healthcare costs for medical and pharmaceutical providers. Additional laboratory tests will increase medical costs; however, this may or may not be substantial given that other bloods tests are being drawn concurrently to check for LDL cholesterol levels. Additionally, the cost spent in testing may be recovered by decreasing the number of

hospitalizations long term. However, testing will qualify more patients to be eligible for drug therapy leading to an increase in prescription costs.

CONCLUSION

Recommendations concerning expanding the use of rosuvastatin to patients with elevated levels of high-sensitivity C-reactive protein without other risks for cardiovascular events must be carefully considered based upon the results of this one study. The absolute risk reduction must justify the additional cost and potential risk of exposing low risk patients to medication. More studies are needed to confirm the benefit of statin therapy in this patient population. Moreover, until studies proving a causative relationship between C-reactive protein levels and cardiovascular events are conducted and confirmed, C-reactive protein testing should only be used as a marker for cardiovascular risk.

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