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REVIEW

Individualized initiation of statin therapy determined by baseline LDL-C: Are you more likely to achieve goal LDL-C?

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Abstract: Cardiovascular disease remains the leading cause of death in the world. A significant amount of clinical data are available to demonstrate the positive influence that 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin) therapy has on slowing the progression of cardiovascular disease and improving clinical outcomes. Achieving the treatment goals for cholesterol in cardiovascular disease continues to present challenges. Recent clinical trial information is available assessing the use of more aggressive initial doses of statin therapy based on initial low-density lipoprotein cholesterol (LDL-C) measurements in an attempt to reach treatment goals sooner. Six clinical trials assessed low-, moderate- and high-risk individuals as well as those with type 2 diabetes mellitus to determine if this treatment approach is both safe and effective. The studies concluded that initial dosing of statin therapy determined by a baseline LDL-C measurement demonstrates good achievement in reaching treatment goals and does not result in a higher rate of adverse effects.

Keywords: LDL-C, statin therapy, treatment goals

Introduction

Cardiovascular disease continues to be the leading cause of death worldwide and coronary heart disease (CHD) accounted for approximately 7.6 million deaths in 2005.[1] Research has revealed that increased low-density lipoprotein cholesterol (LDL-C) significantly contributes to this disease process.[2] Based on these data the National Cholesterol Education Program (NCEP) and the Joint European Societies emphasize LDL-C lowering as a critical step in the management of CHD.[2,3] Recommendations state goal LDL-C level is <100 mg/dL for patients with a history of CHD and for patients having what is considered a risk equivalent to CHD.[2,3] More recent data suggest that although there is strong evidence for a goal LDL-C of <100 mg/dL practitioners should consider a goal of <70 mg/dL for the highest-risk patients.[4,5] Diabetes mellitus is identified as one of the risk equivalents to CHD and the American Diabetes Association endorses the goal LDL-C level of <100 mg/dL for diabetes patients and further states that a goal of <70 mg/dL should be considered for diabetes patients with CHD.[2,3,6]

LDL-C lowering is frequently achieved through the use of 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins). The degree to which statins lower LDL-C varies based on the statin and the dose utilized.[7,8] Current treatment guidelines suggest statin dosing consists of starting an initial dose and then titrating the dose in 6 weeks if the goal LDL-C is not obtained.[2] The largest percentage of statin-induced LDL-C reduction is seen with suggested standard doses. An approximate 6% additional

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reduction is achieved each time the dose is doubled, which may allow a patient to achieve their ultimate goal LDL.[4,8] Dose titration in patients not meeting goal depends on proper follow-up by the patient and practitioners. Surveys of lipid-lowering therapy have suggested a significant percentage of patients are not properly managed. The EUROASPIRE II trial conducted from 1999 to 2000 revealed that of the patients needing lipid-lowering therapy (91.7% on statins) only 49% achieved their cholesterol goal.[9] More recent surveys in other European countries have also demonstrated a significant portion of patients are not reaching goal. The CEPHUS survey revealed 58.5% of patients met the goal LDL-C, with 82.5% of the patients taking statins.[10] High-risk patients needing to achieve a goal LDL-C of <100 mg/dL may pose a problem if their initial LDL-C is significantly elevated. A survey of high-risk patients in a London-based practice showed 38.8% of patients on a statin reached goal LDL.[11] Although it should be noted the goal LDL was <2.0 mmol/L [77 mg/dL] based on the Joint British Societies' guidelines.[11,12]

Concerns about failing to appropriately titrate statins to goal have led to proposals of utilizing higher doses of statins as initial therapy.[7] Data have shown that utilizing higher initial doses of atorvastatin allows more patients to reach their goal LDL-C without compromising safety.[7] Other data have revealed that high dose atorvastatin 80 mg/day has morbidity and mortality benefits vs pravastatin 40 mg/day.[13] A meta-analysis further showed that greater LDL-C lowering was associated with a lower number of cardiovascular events.[14]

Based on these data and the concern for patients not meeting goal LDL-C, it seems prudent to be more aggressive with initial statin dosing and select the initial starting statin dose based on the degree of LDL-C lowering required in each individual patient. Recently several studies have been conducted that utilize dosing algorithms to select the starting dose of atorvastatin. Atorvastatin has been shown to reduce LDL-C levels by 39% to 60% depending on the dose, which ranges from 10 to 80 mg daily.[15] These algorithms select the starting dose based on the patients' baseline LDL and/or CHD risk. This paper reviews these studies and provides discussion on the potential utility of such protocols in clinical practice. The first group of studies evaluates a range of high-risk and low-risk patients, whereas the second group of studies specifically focuses on the high-risk diabetes population.

Data sources

A literature search was conducted using the terms lipid-lowering medications, individualized dosing, algorithm-based dosing of statins, simvastatin, pravastatin, lovastatin, rosuvastatin, atorvastatin, and fluvastatin. MEDLINE, BIOSIS, EBSCOhost, and OVID databases were primary search sites from 2000 to August 2009. All English-based articles and abstracts obtained from the literature searches were reviewed. Additional information was obtained from references cited in the articles.

Clinical evidence

The initial study evaluating use of treatment algorithms with statins was the Atorvastatin Goal Achievement Across Risk Levels (ATGOAL) trial.[16] The baseline characteristics and study design of the ATGOAL trial, as well as the other studies reviewed, are summarized in Table 1. ATGOAL was an 8-week study with a primary endpoint of determining the percentage of patients who reached the LDL-C target with starting doses of atorvastatin based on the baseline LDL-C and CHD risk category. All lipid-lowering medications were discontinued 8 weeks prior to the study. Baseline lipid profiles were obtained after the washout period. Patients were given atorvastatin (dose range 10 to 80 mg/day) based on the LDL-C and risk categories (Table 2). A single dose titration at 4 weeks was available for patients who did not achieve their goal. At 8 weeks, 84.8% (1031/1216) of patients attained their LDL-C target. At 4 weeks, the percentage of patients achieving the LDL-C target was 84.2% (1049/1246). When analyzing the risk categories at 8 weeks, the attainment of goal was 92.9% (299/322) in the low risk group as compared to 84% (199/237) in the medium risk group and 81.1% (533/657) in the high risk group (Table 3). Of the patients completing the study 156 were eligible for a dose titration at week 4; however only 110 of these patients actually had their dose increased with the remainder staying on the original dose per physician discretion. The secondary outcomes are listed in Table 4. A total of 225 patients had an adverse event and 52 (4%) discontinued atorvastatin due to the adverse event. The discontinuation rates for possible, probable or definitely related adverse events were 0.6%, 1.6% and 5.1% in the low-risk, medium-risk and high-risk groups, respectively. Less than 1% had an aspartate aminotransferase (AST) and/or alanine aminotransferase (ALT) elevation greater than 3 times upper limits of normal and there were no documented cases of creatine phosphokinase (CPK) elevation greater than 10 times upper limits of normal.

Two trials were designed using the same methodology but studied patients in different geographical areas.[17,18] The Achieve Cholesterol Targets Fast with Atorvastatin Stratified Titration (ACTFAST)-1 study was conducted in Canada and

Table 1 Clinical trials: study design and patient demographics[16–21]

	ATGOAL[16]	ACTFAST-1[17]	ACTFAST-2[18]	Ducobu et al[19]	Atorvastatin Study Group in Korea[20]	Ferrer-Garcia et al[21]
Study design	Multicenter, open-label, single-step titration	Multicenter prospective, open-label, single dose titration	Multicenter, prospective, open-label, single dose titration	Multicenter, prospective, open-label, single dose titration	Multicenter, prospective, open-label, single dose titration in type 2 diabetes	Prospective, no dose titration, type 2 diabetes
Study duration	8 weeks	12 weeks	12 weeks	12 weeks	8 weeks	24 weeks
Inclusion criteria	Men or non-pregnant women between of 18–80 years, baseline LDL-C 5.6 mmol/L (≤220 mg/dL), TG ≤ 600 mg/dL, and capable of maintaining life-style and dietary modifications	Men or women at least 18 years of age with diagnosed hyperlipidemia and a LDL-C > 2.6 mmo/L (100 mg/dL) along with a screening LDL-C ≤ 5.7 mmol/L (220 mg/dL), TG level of ≤6.8 mmol/L (600 mg/dL) and were considered high risk based on history CHD, CHD equivalent, or estimated 10-year CHD risk >20%	Men or women at least 18 years of age with diagnosed hyperlipidemia and a LDL-C > 2.6 mmo/L (100 mg/dL) along with a screening LDL-C ≤ 5.7 mmol/L (220 mg/dL), TG level of ≤6.8 mmol/L (600 mg/dL) and were considered high risk based on history CHD, CHD equivalent, or estimated 10-year CHD risk >20%	LDL-C of 3.0–6.1 mmol/L (115–235 mg/dL) after 3 months of lipid-lowering diet, TG level <400 mg/dL, ages 30–80 years, and were high CHD risk	Men or women of 18–80 years with hyperlipidemic type 2 diabetes, LDL-C ≥ 130 mg/dL or glycated hemoglobin ≤10% and TG ≤ 400 mg/dL at baseline	Patients were at least 18 years old, had a glycated hemoglobin of ≤10%, TG ≤ 6.8 mmol/L (600 mg/dL) and had a baseline LDL-C of >2.6 mmol/L (100 mg/dL) despite 6 to 12 weeks of dietary treatment
Mean age (years)	55.1 low-risk 58.8 medium-risk 61.6 high-risk	63	61.2	62.1	58.4	61.1
Gender (%)						
Male	58	68	61	70.2	28.9	59.9
Female	42	32	39	29.8	71.1	40.1
Smokers	NR	21%	22.7%	23.3%	NR	29.7%
Diabetes	44% in the high-risk group only	39%	32.7%	34.4%	100%	100%
History of CHD	54% in the high-risk group only	61%	67%	61.9%	NR	NR
Mean baseline LDL-C mmol/L (mg/dL)	4.8 (187) low-risk 4.6 (176) medium-risk 4.1 (160) high-risk	3.9 (151) in statin-free group 3.5 (135) in the statin-treated group	4.1 (159) in statin-free group 3.8 (147) in statin-treated group	4.1 (158)	160.3 ± 22.4	4.10 ± 0.75

Abbreviations: NR, not reported; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; CHD, coronary heart disease.

Western Europe, while the ACTFAST-2 study was in northern and eastern Europe.[17,18] The primary outcome was to assess achievement of LDL-C goal (<2.6 mmol/L [<100 mg/dL]), in high-risk patients, with starting doses of atorvastatin (dose range 10 to 80 mg/day) based on the initial LDL-C baseline value with or without a single dose titration at 6 weeks. At 6 and 12 weeks, the secondary outcomes evaluated were the percentage of patients reaching a total cholesterol/high density lipoprotein-cholesterol (TC/HDL-C) ratio <4 and mean percent change in TC, LDL-C, HDL-C, TC/HDL-C ratio, non-HDL-C, triglycerides (TG), and apolipoprotein-B (apo-B). Safety of atorvastatin was also monitored. The individuals agreed to follow a diet plan. Exclusion criteria was use of a nonstatin lipid-lowering medication in the last

Table 2 Clinical trials: initial dosing protocols of atorvastatin[16–21]

Baseline LDL-C mmol/L (mg/dL)	**ATGOAL study[16]**			
	Low-risk category		**Medium-risk category**	**High-risk category**
	≤1 CHD risk factor	**≥2 risk factors with 10-year CHD risk <10%**	**≥2 risk factors with 10-year CHD risk 10%–20%**	**CHD, CHD equivalent, ≥2 risk factors with 10-year CHD risk >20%**
2.6–3.3 (100–129)	NA	NA	NA	10 mg
3.4–3.6 (130–139)	NA	NA	10 mg	10 mg
3.6–3.9 (140–149)	NA	NA	10 mg	10 mg
3.9–4.1 (150–159)	NA	NA	10 mg	20 mg
4.1–4.4 (160–169)	10 mg	10 mg	10 mg	40 mg
4.4–4.6 (170–179)	10 mg	10 mg	10 mg	80 mg
4.7–4.9 (180–189)	10 mg	10 mg	20 mg	80 mg
4.9–5.7 (190–220)	10 mg	20 mg	20 mg	80 mg
Target LDL-C	<4.1 mmol/L (<160 mg/dL)	<3.4 mmol/L (<130 mg/dL)	<3.4 mmol/L (<130 mg/dL)	<2.6 mmol/L (<100 mg/dL)
	ACTFAST 1 and 2 studies[17,18]			
Baseline LDL-C mmol/L (mg/dL)	**Statin-free group**		**Statin-treated group**	
2.6–3.8 (100–149)	10 mg		20 mg	
3.9–4.1 (150–159)	20 mg		40 mg	
4.2–4.4 (160–169)	40 mg		80 mg	
4.5–5.7 (170–220)	80 mg		80 mg	
	Ducobu et al[19]			
Baseline LDL-C mmol/L (mg/dL)	**Statin-naïve patients**		**Statin-treated patients**	
3.0–4.2 (115–164)	10 mg		20 mg	
4.3–4.5 (165–174)	20 mg		40 mg	
4.5–6.1 (175–235)	40 mg		40 mg	
	Atorvastatin study group in Korea[20]			
Baseline LDL-C mmol/L (mg/dL)				
130–149	10 mg			
150–159	20 mg			
≥160	40 mg			
	Ferrer-Garcia et al[21]			
Baseline LDL-C mmol/L (mg/dL)	**Dose**		**Target reduction in LDL-C level (%)**	
2.6–3.8 (100–147)	10 mg		38	
3.9–4.1 (151–159)	20 mg		46	
4.2–4.39 (162–170)	40 mg		51	
≥4.40 (170)	80 mg		54	

Abbreviations: CHD, coronary heart disease; NA, not-applicable; LDL-C, low-density lipoprotein cholesterol.

2 months, doses of >40 mg/day of any statin and current use of atorvastatin. Patients were divided into a statin-free group (no prior statins within the past 2 months) or a statin-treated group (currently receiving a statin but not achieving LDL-C target goal). The dose assignment of atorvastatin is listed in Table 2.

The ACTFAST-1 study had 1345 patients in the statin-free group and 772 in the statin-treated group.[17] At 12 weeks, 79.6% of statin-free patients achieved the LDL-C target as compared to 58.7% of statin-treated patients. Of those that achieved the target LDL-C goal (n = 1071), 90% in the statin-free group did so with their initial dose. Of the

Table 3 Primary study outcomes[16–21]

Clinical trial	Treatment groups	Proportion of subjects meeting goal (%) (95% CI)			
		LDL-C			
		6 weeks	8 weeks	12 weeks	24 weeks
ATGOAL[16]	Low risk (n = 322)	NR	92.9	NR	NR
	Medium risk (n = 237)	NR	84.0	NR	NR
	High risk (n = 657)	NR	81.1	NR	NR
ACTFAST-1[17]	Statin-free (n = 1345)				
	Atorvastatin 10 mg	84.3 (81.5–87.0)	NR	83.1 (80.3–86.0)	NR
	Atorvastatin 20 mg	83.4 (78.0–88.8)	NR	80.7 (74.9–86.5)	NR
	Atorvastatin 40 mg	88.9 (83.9–93.9)	NR	82.2 (76.2–88.2)	NR
	Atorvastatin 80 mg	79.9 (75.3–84.4)	NR	72.1 (67.0–77.2)	NR
	Statin-treated (n = 772)				
	Atorvastatin 20 mg	55.1 (51.0–59.2)	NR	60.3 (56.3–64.3)	NR
	Atorvastatin 40 mg	55.4 (44.1–66.7)	NR	60.3 (49.1–71.5)	NR
	Atorvastatin 80 mg	58.1 (48.7–67.5)	NR	50.9 (41.5–60.4)	NR
ACTFAST-2[18]	Statin free (n = 341 at wk 6; n = 345 at week 12)				
	Atorvastatin 10 mg	77.8 (71.0–84.6)	NR	75.0 (67.9–82.1)	NR
	Atorvastatin 20 mg	82.0 (71.4–92.7)	NR	78.0 (66.5–89.5)	NR
	Atorvastatin 40 mg	86.5 (71.2–95.5)	NR	79.5 (66.8–92.2)	NR
	Atorvastatin 80 mg	69.1 (60.5–77.7)	NR	68.2 (59.4–77.1)	NR
	Statin-treated (n = 249 at week 6; n = 253 at week 12)				
	Atorvastatin 20 mg	52.4 (44.3–60.5)	NR	67.8 (60.2–75.4)	NR
	Atorvastatin 40 mg	60.7 (42.6–78.8)	NR	62.1 (44.4–79.7)	NR
	Atorvastatin 80 mg	48.1 (36.9–58.2)	NR	46.8 (35.6–57.9)	NR
Ducobu et al[19]	Statin-naïve (n = 215)				
	Atorvastatin 10 mg	NR	NR	NR	NR
	Atorvastatin 20 mg	NR	NR	95.7	NR
	Atorvastatin 40 mg	NR	NR	95.6	NR
Korea study[20]	(n = 149)				
	Atorvastatin 10 mg	NR	87.5	NR	NR
	Atorvastatin 20 mg	NR	86.4	NR	NR
	Atorvastatin 40 mg	NR	93.9	NR	NR
	Atorvastatin 80 mg	NR	66.7	NR	NR
Ferrer-Garcia et al[21]	(n = 202)				
	Atorvastatin 10 mg	NR	NR	NR	75
	Atorvastatin 20 mg	NR	NR	NR	67
	Atorvastatin 40 mg	NR	NR	NR	51
	Atorvastatin 80 mg	NR	NR	NR	59

Abbreviations: LDL-C, low-density lipoprotein cholesterol; NR, not reported.

435 patients reaching goal in the statin-treated group, the target LDL-C was achieved with atorvastatin at 20 mg (72%), 40 mg (64%) and 80 mg (96%). In the patients reaching goal in the statin-free group, titration was necessary with the doses of 10 mg (n = 106), 20 mg (n = 30) and 40 mg (n = 17) and target LDL-C was achieved in 58%, 67% and 69%, respectively. Dose titration was needed in the statin-treated group with target LDL-C achieved in 42% with the initial dose of 20 mg (n = 260) and 52% with the initial dose of 40 mg (n = 33). Of note, up to 20% of patients in each

Table 4 Secondary study outcomes[16–21]

Clinical trial	Treatment groups	Percentage mean reduction of lipid parameters from baseline							Proportion of subjects
		LDL-C	TC	TG	HDL-C	TC/HDL-C	Apo-B	Non-HDL-C	TC/HDL-C ratio target <4
ATGOAL[16]	Low-risk group (n = 335)	–39.1	–29.0	–18.6	–2.2	NR	NR	–31.2	NR
8-week	Medium-risk group (n = 249)	–36.8	–28.7	–20.9	1.7	NR	NR	–31.4	NR
results	High-risk group (n = 699)	–44.6	–35.0	–23.5	–2.4	NR	NR	–34.4	NR
ACTFAST-1[17]	Statin-free (n = 1345)								
12-week results	Atorvastatin 10 mg	–34.8	–23.9	–13.7	3.1	–25.4	–31.5	–32.1	83.1
	Atorvastatin 20 mg	–43.8	–31.6	–22.7	1.4	–32.0	–39.4	–41.0	85.9
	Atorvastatin 40 mg	–49.8	–37.2	–26.5	1.6	–37.4	–44.8	–47.1	86.9
	Atorvastatin 80 mg	–52.7	-39.7	–5.2	0.6	–39.1	–46.8	–48.7	79.1
	Statin-treated (n = 772)								
	Atorvastatin 20 mg	–21.4	–15.3	–8.2	1.0	–15.4	–21.2	–20.4	79.3
	Atorvastatin 40 mg	–37.0	–27.5	–22.8	0.6	–27.3	–34.2	–35.2	78.4
	Atorvastatin 80 mg	–41.0	–32.0	–18.9	–2.7	–29.5	–38.0	–39.1	70.6
ACTFAST-2[18]	Statin-free (n = 347)								
12-week results	Atorvastatin 10 mg	–33.6	–23.6	–9.9	4.2	–24.6	–31.6	–31.2	77.8
	Atorvastatin 20 mg	–40.5	–28.4	–12.3	2.3	–29.3	–36.0	–36.8	80.8
	Atorvastatin 40 mg	–49.1	–36.4	–15.0	–3.7	–32.9	–44.3	–45.1	84.6
	Atorvastatin 80 mg	–49.4	–39.2	–21.9	–3.2	–36.3	–44.5	–47.1	75.0
	Statin-treated (n = 253)								
	Atorvastatin 20 mg	–24.7	–17.4	–3.8	–2.7	–13.3	–22.5	–21.9	71.2
	Atorvastatin 40 mg	–36.6	–27.0	–19.9	4.1	–28.3	–33.1	–34.8	82.8
	Atorvastatin 80 mg	–40.2	–30.8	–19.5	–1.4	–29.1	–36.3	–37.7	66.7
Ducobu et al 12-week results[19]	Statin-naïve (n = 215) (Data NR based on dose)	–45.9	–32.4	NR	0.04	NR	NR	NR	NR
Korea study 8-week results[20]	Atorvastatin 10 mg (n = 56)	–42.5	–30.3	–19.3	2.8	NR	NR	–38.9	NR
	Atorvastatin 20 mg (n = 22)	–52.9	–37.5	–32.6	4.0	NR	NR	–49.4	NR
	Atorvastatin 40 mg (n = 65)	–58.7	–45.0	–20.9	–5.2	NR	NR	–53.0	NR
	Atorvastatin 80 mg (n = 6)	NR	NR	NR	NR	NR	NR	NR	NR
Ferrer-Garcia et al[21]	Atorvastatin 10 mg (n = 75)	–16.5	–21.6	–12.3	–3.0	NR	NR	–27.1	NR
24-week results	Atorvastatin 20 mg (n = 61)	–35.6	–28.5	–18.0	–1.8	NR	NR	–36.7	NR
	Atorvastatin 40 mg (n = 35)	–35.5	–29.8	–26	–0.2	NR	NR	–38.2	NR
	Atorvastatin 80 mg (n = 17)	–55.7	-49.0	–32.5	–7.2	NR	NR	–56.7	NR

Abbreviations: NR, not reported; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; TC/HDL-C, total cholesterol/low-density lipoprotein-cholesterol; Apo-B, apolipoprotein B; non-HDL-C, non-high-density lipoprotein cholesterol.

group that met criteria for dose titration did not actually receive an increased dose. Reasons why some patients did not have a dose titration were failure of investigator to follow protocols (n = 23), patient not following directions (n = 28) and adverse events (n = 7). The primary and secondary efficacy outcomes are summarized in Tables 3 and 4.

The incidence of adverse events with all doses of atorvastatin was 12.1%.Adverse events were asthenia (1.6%), myalgia (1.4%), constipation (1.1%), dyspepsia (1.1%), elevated AST/ALT > 3 times upper limit, regardless of causality (1.2%), and one case of elevated CPK > 10 times the upper limit of normal. Of note, this patient did not report myalgia

and had 2 falls 2 days prior due to a previous condition unrelated to statin therapy.

The ACTFAST-2 study results revealed 73.5% of patients in the statin-free group (n = 347) and 60.5% in the statin-treated group (n = 253) achieved the LDL-C target at 12 weeks.[18] At week 6, 391 patients had attained the primary outcome. The majority of subjects who reached goal achieved the target LDL-C by week 6 (96%). Dose titration results were not reported because so few subjects met criteria for dose titration. The primary and secondary outcomes are summarized in Tables 3 and 4. The most frequently reported adverse events were diarrhea (0.5%), nausea (0.5%), elevated AST/ALT (0.8%) and myalgia (0.7%). Twelve patients discontinued therapy.

The primary endpoint of the 12-week study by Ducobu et al was to determine the proportion of patients achieving their LDL-C goal with starting doses of atorvastatin (10 to 40 mg/day) based on LDL-C levels.[19] A single dose titration was allowed at week 6 by doubling the dose of atorvastatin if the goal LDL-C was not obtained. Secondary endpoints were mean percentage change in TC, LDL-C, HDL-C, and TG at weeks 6 and 12 along with proportion concomitantly reaching LDL-C and TC targets at week 12. Other secondary endpoints assessed were the proportion of patients reaching goal LDL-C at 6 weeks along with different LDL-C strata achieving LDL-C control at 6 and 12 weeks, proportion of diabetes patients achieving LDL-C control at 12 weeks and C-reactive protein (CRP) at baseline and at weeks 6 and 12. All patients were counseled on the Therapeutic Lifestyle Changes diet.[2] Medication-related exclusion criteria was use of nonstatin lipid-lowering medications (fibrates, resins, or acipimox) or atorvastatin during the last two months and higher maintenance doses of other statins such as >40 mg/day of simvastatin, fluvastatin or pravastatin. Patients were divided into two treatment groups; statin-naïve (n = 215) and previously treated with a statin (n = 11). Due to the low overall number of patients in the previous statin treatment arm, the results in those subjects were not reported. Dosing of atorvastatin is listed in Table 2. In the statin-naïve group, 95.4% (95% CI 91.4% to 97.9%) reached their LDL-C goal at 6 weeks. Dose titration was required in 4.6% of patients. At 12 weeks, 96.4% (95% CI 92.7% to 98.5%) of the statin-naïve group reached the goal. Response rates did not vary based on the different starting dose subgroups. A secondary endpoint reported, with the statin-naïve group, was a mean standard deviation change in CRP of –1.7 (9.3) mg/L and –1.4 (9.1) mg/L at weeks 6 and 12, respectively. The mean percentage standard deviation change in the CRP was 5.2 (156.1) and 29.4 (253.8) at weeks 6 and 12. At 12 weeks, 97.1% of diabetes patients reached the LDL-C goal as compared to 95.6% of the nondiabetes patients. Overall 32.8% of patients reported an adverse event with headache, abdominal pain, diarrhea, and upper respiratory infection being the most commonly reported, occurring in 2.2% of patients. Although 3.4% of patients withdrew from the study due to an adverse event, no serious adverse events were related to atorvastatin treatment.

Clinical evidence in type 2 diabetes patients

The Atorvastatin Study Group in Korea evaluated the flexible dosing of atorvastatin (dose range 10 to 40 mg/day) based on the LDL-C in type 2 diabetes patients.[20] The primary outcome was the percentage of patients meeting the goal LDL-C of 100 mg/dL following 8 weeks of therapy. Additional measurements were the percentage change over 8 weeks in HDL-C, TG, TC, non-HDL, ratio of LDL to HDL and non lipid-lowering effects such as flow-mediated endothelium-dependent dilation (FMD), flow-mediated endothelium independent dilation (EID) and plasminogen activator inhibitor type 1 (PAI-1). A 4-week washout period was done with any lipid-lowering agent prior to enrollment. Baseline lipid parameters and glycated hemoglobin were obtained. Medication-related exclusion criteria were previous use of niacin or fibrates. Continuation of the patient's diet and exercise plan was recommended during the study. The atorvastatin dosing protocol is listed in Table 2. At the end of 4 weeks, a dose titration could occur if the target LDL-C of 100 mg/dL was not met. Of the 209 enrolled patients, 149 completed the study. At 4 weeks, the percentage of patients reaching LDL-C goal was 90.3%, 88.9% and 91.3% when receiving 10 mg, 20 mg and 40 mg, respectively. At 8 weeks, the overall percentage of patients attaining the goal was 89.3% (95% CI 84.3% to 94.2%, Chi-square test $P = 0.1722$). Fourteen patients (9.4%) had a dose titration at 4 weeks. A dose-dependent statistically significant decrease occurred with LDL-C, TG and non-HDL-C ($P < 0.0001$). The pre- and post-treatment values for FMD improved ($P = 0.0001$) but the EID and PAI-1 did not reach statistical significance. The initial 209 patients were analyzed for safety of atorvastatin. Adverse events were abdominal pain (2.9%), increased ALT (2.4%), dizziness (1.9%), headache/dyspepsia (1.4%), and increased CK (1.4%). Ten patients withdrew from the study due to adverse events, but no events were reported to be serious.

Ferrer-Garcia et al studied the dose assignment of atorvastatin (10–80 mg/day) to the baseline LDL-C in

statin-naïve type 2 diabetes patients.[21] The primary efficacy outcome, at 24 weeks, was the percent of patients achieving the LDL-C target of less than 2.6 mmol/L (100 mg/dL) without a dose titration. The mean percent change in TC, LDL-C, HDL-C, non-HDL-C, and TG were assessed. All patients were instructed on diet. The dosage assignment is listed in Table 2. The overall proportion achieving the target was 66.5% (125/188) with an overall mean LDL-C reduction of 35% ($P < 0.001$). Results based on atrovastatin dose are listed in Table 3. The percent of change was statistically significant ($P < 0.05$) for TC (–32.2%), HDL-C (–3%), TG (–22.2%) and non-HDL-C (–39.7%) (see Table 4). The adverse events that led to 2 patients withdrawing from the study were elevated liver enzymes (80 mg group) and slight muscular pain (20 mg group).

Discussion

The clinical outcome benefits of using statins in patients with elevated cholesterol, with significant risk for coronary artery disease, or with known coronary artery disease have been well documented over the years by numerous clinical trials. Despite these known beneficial effects, it often takes a significant period of time to reach the desired cholesterol lowering goal or the goal is never reached at all. The studies described in this review looked at alternative, aggressive dosing schemes to initiate statin therapy to determine if the cholesterol-lowering goals can be achieved and if they can be achieved in a shorter time frame. The proposed theory is that achieving the LDL-C cholesterol goal in a shorter period of time may have a significant impact on long-term outcomes.

In the studies reviewed, various dosing approaches were utilized. In the ATGOAL trial, the initial atorvastatin dose was based on a baseline LDL-C measurement and cardiovascular risk categories combined.[15,16] This dosing approach, which allowed 1 dose titration at 4 weeks, led to 84.8% of patients reaching their LDL-C goal at the end of the 8-week trial. The adverse event rate in this trial was relatively low, with an overall atorvastatin discontinuation rate of 4% due to adverse events. The ATGOAL trial demonstrated a high achievement of the LDL-C goal in a relativity short period of time which was well tolerated.

The ACTFAST-1 and -2 studies utilized a dosing regimen in which the initial atorvastatin dose was based on a baseline LDL-C measurement alone.[17,18] A one-time dosage titration was allowed at 6 weeks during the 12-week trials if a patient had not reached their LDL-C goal. The treatment groups were divided into statin-free and statin-treated. In the ACTFAST-1 trial, the percent of patients achieving their LDL-C goal was higher in the statin-free group, 79.6%, compared to the statin-treated patients, 58.7%.[17] Interestingly, 90% of the patients achieving their LDL-C goal in the statin-free group did so with their initial atorvastatin dose. This suggests that if a patient is going to respond well in achieving their LDL-C goal, an initial aggressive dose will likely result in this goal being reached. For those who have been previously on statin therapy and not achieved their LDL-C goal, in most cases, a dose titration will not always be adequate to assist them in achieving their LDL-C goal. The overall incidence of adverse events due to atorvastatin was 12.1%, with myalgias and significantly elevated liver enzymes occurring in 1% to 2% of patients. Only 1 case of elevated CPK was reported, demonstrating that this dosing approach was relatively well tolerated.

The ACTFAST-2 trial results were similar to those seen in the ACTFAST-1 study.[18] In the statin-free treatment group, 73.5% of patients achieved their LDL-C goal at 12 weeks, compared to 60.5% of patients achieving their LDL-C goal in the statin-treated group. Similar to the ACTFAST-1 study, 96% of the subjects who reached their LDL-C goal did so in the first 6 weeks of the 12-week trial. This again suggests that, if a patient is going to respond to statin therapy and reach the desired goal, this response will typically occur early on in therapy, if the initial dose is aggressive. Atorvastatin was well tolerated in this trial, with elevated liver enzymes and myalgias reported in less than 1% of subjects.

Similar to the trials just mentioned, the Ducobu study utilized an initial LDL-C measurement to determine an initial starting dose for atorvastatin.[19] In addition, a one-time dosage titration was allowed midway through (at 6 weeks) of the study. Patients were categorized as statin-naïve and previously treated with a statin in the analysis, with only the statin-naïve group being reported in the study results. In the statin-naïve patient group, 95.4% achieved their LDL-C treatment goal at 6 weeks. At 12 weeks, the percentage of statin-naïve patients achieving their LDL-C goal only increased to 96.4%. Of note, the LDL-C treatment goal in this trial was less than 115 mg/dL, which is higher than the current recommendations. These results again demonstrated that if patients with elevated LDL-C are being treated with aggressive doses of atorvastatin, the response to achieving the LDL-C treatment goal occurs relatively soon with the initial dose. Dosage titration in those not achieving their LDL-C with initial aggressive dosing is not likely to result in their achieving that LDL-C goal.

The Atorvastatin Study Group in Korea assessed a sliding scale dosing approach based on initial LDL-C measurements in patients with type 2 diabetes mellitus.[20] This study allowed 1 dosage titration midway through the study at 4 weeks. At the end of the trial, 89.3% of patients achieved their LDL-C treatment goal. Only 9.4% of the patients in this study had dosage titration at 4 weeks of the study. In addition to evaluating the LDL-C treatment goal, the investigators evaluated pre- and post-values of FMD, EID, and PAI-1. Of these three measurements, only the post-FMD demonstrated an improvement over the pre-FMD measurement. The clinical significance of these three measurements and how they affect long-term clinical outcomes remain to be determined. From a safety standpoint, atorvastatin was well tolerated, with increases in ALT and CK reported in a small percentage of patients. Similar to the other studies, very few study subjects required a dosage titration, supporting the theory that this initial aggressive dosing strategy results in a majority of patients achieving the LDL-C goal with the initial dose.

The last study reviewed looked at a sliding scale dosage initiation based on a baseline LDL-C measurement in statin-naïve patients with type 2 diabetes mellitus.[21] As noted in the trial description, dosage titration was not allowed in this trial. At the conclusion of this trial at 24 weeks, only 66.5% of the patients achieved their LDL-C treatment goal. The adverse event rate was very low with only 3 patients dropping out due to atorvastatin adverse events. This trial is not consistent with the results seen in the previous trials, in that fewer patients in this trial achieved their LDL-C treatment goal with the initial statin dosage regimen. It is difficult to determine if this difference is due to the study population or relative differences in the aggressiveness of the dosage regimens.

When comparing these trials, several difficulties were encountered. The initial dosage of atorvastatin differed based on the initial baseline LDL-C measurement, which makes head-to-head comparisons of these trials and their results complex. An additional difficulty is that two of these studies included only type 2 diabetes mellitus patients, which may be an unfair comparison to the other studies that did not included a solely diabetes mellitus population. The ATGOAL study was the only trial that included low and high risk patient populations.[16] This trial also demonstrated a good rate of achievement in reaching the LDL-C treatment goal. Therefore, this dosing scheme would seem to be appropriate to implement into general clinical practice.

Collectively, the studies that were identified looking at initial dosing of statins in relationship to baseline LDL-C measurements demonstrated that a significant percentage of patients achieved their LDL-C goal during the duration of the study.[16–21] In addition, it is noteworthy that a majority of patients enrolled in these trials reached their LDL-C treatment goal with the initial dosage of atorvastatin. Patients who had higher baseline LDL-C levels, which are typically the most difficult to get to goal, were initially started on a higher dose of atorvastatin. This demonstrates that if a patient is going to achieve their LDL-C treatment goal, the response with initial dosing will be relatively quick, within 4 to 6 weeks. The percentage of patients meeting their LDL-C treatment goal after dosage titration was relatively small; therefore for patients not achieving the LDL-C treatment goal with this initial dosing strategy, an alternative pharmacologic combination or approach should be considered. The anticipated reductions in LDL-C levels that have been demonstrated in clinical trials are 38%, 46%, 51%, and 54% reductions with 10 mg, 20 mg, 40 mg, and 80 mg of atorvastatin, respectively.[8]

In addition to the primary goal of these trials, several of the trials evaluated secondary goals.[16–21] Total cholesterol, TG, HDL-C, TC/HDL-C ratio, Apo-B, and non-HDL-C were utilized as secondary goals in these trials. Reductions in TC, TG, TC/HDL-C ratio, Apo-B, and non-HDL-C were observed in the trials assessing these outcomes. The effect in these studies of these dosing schemes on HDL-C was mixed.

One of the major limitations of the studies was that they were relatively short, ranging from 8 to 24 weeks.[16–21] Since these trials were short, long-term outcomes such as reduced coronary events, mortality and other long-term outcome measures could not be assessed. Therefore, these studies were limited to using LDL-C lowering and other cholesterol profile markers as their major outcomes to determine if these dosing approaches were indeed effective in getting more people to goal in a shorter time. Based on the studies reviewed, it is evident that a larger percentage of patients achieved their LDL-C treatment goal in a time compared to traditional initiation and dosage titration of statin therapy. However, it remains to be seen whether or not this more aggressive approach of initiating statin therapy has any additional impact on long-term clinical outcomes.

A potential safety concern with this approach to the initiation of statin therapy is the possibility of a higher incidence of significant adverse effects. In the studies reviewed, the rate of adverse effects was relatively low and not higher

than expected with traditional dosing of starting at a low dose and slowly titrating the dose up until the treatment goal is achieved. Choosing a more aggressive starting dose of a statin does not appear to cause a significantly higher rate of adverse reactions.

An additional limitation was that all of the studies identified and reviewed for initial aggressive dosing used only atorvastatin. It may not be appropriate to assume that this aggressive initial dosing will be as safe and efficacious with other statins. Studies assessing aggressive initial dosing of other statins should be conducted instead of trying to extrapolate these data to other drugs in this class.

Although the main focus of this review is on the statin therapy and dosing algorithm, it is important to remember the importance of diet therapy in patients with hyperlipidemia and coronary heart disease. As noted in the review of these trials, appropriate diet therapy was utilized, and clinicians should incorporate an appropriate diet as a part of the treatment approach.

It is difficult to take these studies as a whole and incorporate into practice an approach to initiating statin therapy. The main reasons this is difficult are that these trials did not utilize the same criteria and approach for determining the initial statin dose, and that some of the trials included patients who were already being treated with a statin.

The ATGOAL trial utilized a relatively complex approach to initiating statin therapy compared to the other studies that were identified and reviewed. In addition to utilizing the baseline LDL-C measurement, subjects were risk stratified based on their CHD risk, and then the initial statin dose was determined taking both of these factors into account. It could be argued that this approach is too complex in practice for the general clinical setting. However, this approach would likely be very useful in a specialized setting in which initiation of statin therapy was the major focus of the clinical practice, for example, a specialized lipid clinic.

Of the trials identified and reviewed, the dosing initiation algorithm that appeared to be the most user friendly for general practitioners as well as effective in achieving the LDL-C goal was that utilized in the ACTFAST-1 and -2 trials.[17,18] Specifically, the "statin-free" treatment algorithm could be utilized and incorporated into most clinical settings and practices. This algorithm demonstrated achievement of the LDL-C goal in approximately 70% to 80% of the subjects by the end of the 12-week trial. In addition, this dosing approach was well tolerated, with minimal adverse effects reported.

Conclusion

Cardiovascular disease remains the leading cause of death in the world and has a significant impact on healthcare systems. Historically, the utilization of statins in the cardiovascular disease population has demonstrated a significant impact on clinical outcomes, specifically reduced mortality and reduced progression of cardiovascular disease and cardiovascular disease complications. Despite this evidence, many patients with cardiovascular disease either do not receive statin therapy, or are on suboptimal doses, as the medications are not uptitrated to achieve the treatment goals. The clinical trials reviewed assessed the efficacy and safety of using an initial dosing strategy determined by baseline LDL-C measurements to achieve treatment goals quicker. The studies demonstrated that some of the dosing strategies worked very well in reaching cholesterol treatment goals and were also well tolerated. The question that remains unanswered is what impact does achieving treatment goals sooner have on long-term clinical outcomes. Initial dosing of statin therapy with an algorithm utilizing a baseline LDL-C measurement appears to be a safe and effective option for starting a patient on statin therapy.

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