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https://doi.org/10.1007/s00417-019-04464-2

RETINAL DISORDERS

Natural history of diabetic macular edema and factors predicting outcomes in sham-treated patients (MEAD study)

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Received: 15 May 2019 / Revised: 25 August 2019 / Accepted: 4 September 2019

Abstract

Purpose To describe the natural history of diabetic macular edema (DME) with respect to best-corrected visual acuity (BCVA) and central retinal thickness (CRT) outcomes and to identify baseline patient characteristics and systemic factors associated with improvement or worsening of outcomes in sham-treated patients.

Methods The study population was sham-treated patients ($n = 350$) in the 3-year MEAD registration study of dexamethasone intravitreal implant for treatment of DME. Patients had center-involved DME and received sham intravitreal injections in the study eye at ≥ 6-month intervals. Potential prognostic factors for outcomes were evaluated using multiple linear regression analysis.

Results Visual and anatomic outcomes were poorer in patients who left the study early ($n = 198$) than in study completers ($n = 152$). Mean change in BCVA from baseline at the last visit with available data was + 0.9 letters; 37.5% of patients had no change in BCVA, 23.2% had gained > 10 letters, and 16.0% had lost > 10 letters. Older age and baseline diabetic retinopathy score > 6 were associated with worse BCVA outcomes; thicker baseline CRT and larger number of hypertension medications used were associated with larger reductions in CRT during the study.

Conclusions BCVA and CRT outcomes were variable in this population of DME patients with generally good glycemic control. In DME patients without active treatment, older age and baseline diabetic retinopathy score > 6 were associated with less improvement in BCVA; thicker baseline CRT and a larger number of antihypertensive medications used predicted better improvement in CRT.

Trial registration The MEAD study trials are registered at ClinicalTrials.gov with the identifiers NCT00168337 and NCT00168389.

Keywords Diabetic macular edema · Natural history · Prognosis · Risk factors · Visual acuity

MEAD study group members are listed in Appendix 1.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00417-019-04464-2) contains supplementary material, which is available to authorized users.

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Published online: 25 October 2019

Introduction

Diabetic macular edema (DME) is a manifestation of diabetic retinopathy (DR) and the major cause of central vision loss among patients with DR. The pathogenesis of DME, although not completely understood, is believed to involve multiple interacting pathways related to hyperglycemia [1]. Free radical and advanced glycation end products, inflammatory processes, and vascular endothelial growth factor (VEGF) have all been implicated in the breakdown of the blood-retinal barrier that results in vascular leakage and retinal thickening in DME [1, 2]. A moderate negative correlation has been demonstrated between central retinal thickness (CRT) measured on optical coherence tomography (OCT) and best-corrected visual acuity (BCVA) in patients with DME [3].

Several systemic risk factors for the development of DME have been identified. A meta-analysis of results from 20 population-based studies, in which DR and DME were determined from fundus photographs using consistent, rigorous methods, identified a longer duration of diabetes, higher glycosylated hemoglobin (HbA1c) levels, and hypertension as significant risk factors for DME in adults with diabetes [4]. There was also an association between higher blood cholesterol levels (total cholesterol ≥ 4 mmol/L) and a higher prevalence of DME [4]. Total-to-HDL (high-density lipoproteins) ratio and LDL (low-density lipoproteins) have also been shown to be significant risk factors for the development of DME [5]. Consistent with these findings, in a recent study using a health claims database, lipid-lowering medication use was associated with a decreased incidence of DME [6]. Other potential systemic risk factors for DME include age, sleep apnea, pregnancy, anemia, lack of glycemic control, duration of diabetes, nephropathy/microalbuminuria, systemic fluid retention in congestive heart failure or renal disease, and use of the glitazone (thiazolidinedione) class of oral antihyperglycemic medications [7–11].

Systemic factors such as lack of glycemic control might also be associated with the severity of DME and with visual and anatomic outcomes after treatment. In a prospective study in 52 patients with DME, higher HbA1c was associated with both worse CRT and worse BCVA [12]. Higher HbA1c was also associated with worse CRT after surgical treatment (pars plana vitrectomy with internal limiting membrane peeling) of 44 eyes with DME [13]. In a retrospective series of 124 patients with DME treated with anti-VEGF therapy, patients with lower HbA1c at baseline demonstrated better improvement in both BCVA and CRT after anti-VEGF treatment [14]. However, in the RISE/RIDE registration studies of ranibizumab for treatment of DME, no associations were found between baseline systemic factors (including HbA1c and blood pressure) and BCVA improvement after 24 months of treatment [15]. Baseline HbA1c in the RISE/RIDE studies was required to be ≤ 12% [16], and there were no differences in outcomes among ranibizumab-treated patients in the 4 quartiles of baseline HbA1c (≤ 6.6%, > 6.6 to 7.4%, > 7.4 to 8.5%, and > 8.5%) [17].

Current therapy for diabetes aims for glycemic control and management of hypertension and serum lipids to decrease the risk of complications including DME [18]. However, the extent to which systemic factors such as hypertension and hyperlipidemia might exacerbate pre-existing DME has not been well studied. The objectives of this study were to describe the natural history of DME with respect to BCVA and CRT outcomes and to identify baseline patient characteristics and systemic factors that are associated with improvement or worsening of outcomes in patients with no active treatment. The study population was the sham treatment group of the 3-year MEAD registration study [19] of dexamethasone intravitreal implant for treatment of DME.

Methods

This was a post hoc analysis of efficacy outcomes and factors associated with efficacy outcomes in patients assigned to the sham group in the 3-year, randomized, multicenter, double-masked registration study (MEAD) of dexamethasone intravitreal implant for treatment of DME. The MEAD study was conducted from February 2005 to June 2012 at 131 sites in 22 countries. The study comprised two trials (ClinicalTrials.gov NCT00168337 and NCT00168389) with identical protocols, and the results were pooled for analysis. The study methods and patient selection were reported previously [19–22] and are described briefly below. The study was conducted in accordance with the principles of the Declaration of Helsinki, and the study protocol was approved by an institutional review board or independent ethics committee at each site. All patients provided written informed consent.

Patients included in the study were adults diagnosed with type 1 or 2 diabetes mellitus and fovea-involved macular edema. BCVA in the study eye, measured with the Early Treatment Diabetic Retinopathy Study (ETDRS) method, was required to be between 34 and 68 letters (20/200 and 20/50), and CRT in the 1-mm central macular subfield of the study eye was required to be ≥ 300 μm on time-domain OCT. Key exclusion criteria included uncontrolled diabetes (HbA1c > 10%) or other systemic disease, glomerular filtration rate (GFR) < 50 mL/min, treatment with intravitreal anti-VEGF within the 3 months before study entry, treatment with intravitreal triamcinolone within the 6 months before study entry, intraocular laser treatment within the 90 days before study entry, a history of pars plana vitrectomy in the study eye, and active iris or retinal neovascularization in the study eye.

Patients in the sham group received sham procedure (a needleless implant applicator was pressed against the conjunctiva of the study eye) no more frequently than every

6 months. Patients were followed for 36 or 39 months. All patients who required rescue treatment in the study eye were exited from the study before receiving the rescue treatment. Patients who had a loss in BCVA from baseline of 15 or more letters in the study eye, which was confirmed at two consecutive visits at least 4 weeks apart, were exited from the study at the discretion of the investigator. The main efficacy measures were BCVA in the study eye, measured with the ETDRS method at every study visit, and CRT in the 1-mm central macular subfield of the study eye, measured with time-domain OCT (Stratus OCT2 or OCT3) every 3 months. OCT images were evaluated by a central reading center (University of Wisconsin Fundus Photograph Reading Center, Madison, WI). DR was graded using the ETDRS Final Retinopathy Severity Scale [23] condensed to 9 severity categories [21], with scores of ≤ 6 representing severity up to severe nonproliferative DR (NPDR) and scores > 6 representing mild proliferative DR (PDR) or worse severity.

All analyses in the present report used observed values, with no imputation for missing values, in the intent-to-treat population. Visual outcomes analyzed in study eyes were mean change in BCVA from baseline at each study visit, percentage of patients with at least 15-letter improvement in BCVA, distribution of patients by BCVA change from baseline (> 10-letter gain, 5–10-letter gain, no change [< 5 letters gain or loss], 5–10-letter loss, or > 10-letter loss), and average change in BCVA from baseline during the study period evaluated with the time-adjusted area-under-the-curve (AUC) approach. Anatomic outcomes evaluated in study eyes were mean change in CRT from baseline at each study visit, percentage change in CRT from baseline in patients stratified by baseline CRT (≤ 400 or > 400 μm), percentage of patients with CRT < 300 μm, and percentage of patients with at least two-step progression in DR severity from baseline. Additional analyses compared blood pressure, HbA1c, and GFR change from baseline at study exit between patients who discontinued from the study and patients who completed the study. Time to discontinuation because of lack of efficacy was evaluated with Kaplan–Meier survival analysis.

Multiple linear regression analysis was used to evaluate potential prognostic factors of BCVA change from baseline to the last available visit, average BCVA change from baseline during the study (AUC approach), and CRT change from baseline at the last available visit. The final models were developed using the stepwise selection method with the entry *P* value criterion set at 0.10. The variables evaluated as potential factors in the models were baseline patient characteristics including demographics (age, race, gender), body mass index (BMI), HbA1c (≤ 8% vs > 8%), systolic blood pressure, diastolic blood pressure, GFR, duration of diabetes, history of hypertension, and history of hypercholesterolemia; baseline study eye characteristics including lens status, DR severity (≤ 6 vs > 6), duration of DME, previous treatment for DME, and BCVA (in the models for BCVA change from baseline) or CRT (in the model for CRT change from baseline); and parameters during the study including use of aspirin or other platelet aggregation inhibitor, use of glitazone, use of medication to treat dyslipidemia, adverse event reports of dyslipidemia (blood cholesterol increased, blood triglycerides increased, low-density lipoprotein increased, hypercholesterolemia, dyslipidemia, hyperlipidemia, or hypertriglyceridemia), number of antihypertensive medications used, and change in HbA1c from baseline at the last visit. Platelet aggregation inhibitors, glitazones, medications used to treat dyslipidemia, and antihypertensive medications are listed in Appendix 2. All analyses were performed using SAS software version 9.3 (SAS Inc., Cary, NC).

Results

Baseline characteristics of the 350 patients in the sham group of the MEAD study are listed in Table 1. The attrition rate was high in large part because of the requirement for patients to exit the study before receiving rescue treatment. Within the sham group, 152 (43.4%) patients completed the 3-year study and 198 (56.6%) patients discontinued from the study; the most common reason for early exit from the study was lack of efficacy (84 [24.0%] patients). Kaplan–Meier analysis indicated that the rate of discontinuations because of lack of efficacy was highest at months 6 and 12 (Fig. 1).

Analysis of blood pressure, HbA1c, and GFR change from baseline at the last available visit showed no clinically significant differences in these parameters between sham patients who left the study early ($n = 198$) and sham patients who completed the study ($n = 152$) (Table 2). In contrast, visual and anatomic outcomes at the last available visit were poorer in patients who left the study early than in patients who completed the study (Table 2). At baseline, patients who left the study early and patients who completed the study had similar mean BCVA (56.7 and 57.2 letters, respectively) and CRT (476 and 442 μm, respectively). However, at the last available visit, mean BCVA was 54.1 and 62.0 letters, respectively, and mean CRT was 458 and 308 μm, respectively (Table 2).

Mean (median) HbA1c for all patients was 7.5% (7.3%) at baseline ($n = 349$) and 7.8% (7.6%) at the study end ($n = 147$).

Visual outcomes

Analysis of the mean change in BCVA from baseline at scheduled study visits showed a small but significant improvement in BCVA in sham-treated patients throughout the study. Mean changes in BCVA from baseline were similar regardless of baseline lens status (phakic or pseudophakic) (Fig. 2a). The mean improvement in BCVA was approximately 1–3 letters during the first 12 months of the study and increased during

Table 1 Baseline patient characteristics

Characteristic	Patients ($n = 350$)
Age, mean (SD), years	62.5 (9.5)
[Range]	[26–88]
Male, *n* (%)	217 (62.0)
Race/ethnicity, *n* (%)	
Asian (excludes Japanese)	53 (15.1)
Black	20 (5.7)
Caucasian	233 (66.6)
Hispanic	33 (9.4)
Japanese	1 (0.3)
Other	10 (2.9)
Height, mean (SD), cm	165.9 (9.2)
Weight, mean (SD), kg	80.5 (17.6)
Type of diabetes	
Type I	28 (8.0)
Type II	322 (92.0)
Duration of diabetes, mean (SD), years	15.9 (9.1)
HbA1c, mean (SD), %	7.5 (1.1)
≤ 8%, *n* (%)	249 (71.1)
> 8%, *n* (%)	100 (28.6)
Data not available	1 (0.3)
Glomerular filtration rate, mean (SD), mL/min	86.8 (25.6)
Systolic blood pressure, mean (SD), mm Hg	137.2 (17.2)
Diastolic blood pressure, mean (SD), mm Hg	78.5 (10.2)
History of hypertension, *n* (%)	258 (73.7)
History of hypercholesterolemia, *n* (%)	93 (26.6)
BCVA in study eye, mean (SD), ETDRS letters	56.9 (8.7)
CRT in study eye, mean (SD), μm	460.9 (132.6)
Duration of DME in study eye, mean (SD), months	25.9 (27.3)
[Range]	[0–187]
Previous treatment for DME in study eye, *n* (%)	
Focal/grid laser	243 (69.4)
Intravitreal steroid	61 (17.4)
Anti-VEGF	26 (7.4)
None	89 (25.4)
DME perfusion status in study eye	
Ischemic	27 (7.7)
Non-ischemic	284 (81.1)
Data not available	39 (11.1)
DR severity score in study eye, *n* (%)	
≤ 6 (severe NPDR or better)	200 (57.1)
> 6 (mild PDR or worse)	123 (35.1)
Data not available	27 (7.7)
Lens status in study eye, *n* (%)	
Phakic	249 (71.1)
Pseudophakic	101 (28.9)

BCVA best-corrected visual acuity, *BMI* body mass index, *CRT* central retinal thickness, *DME* diabetic macular edema, *DR* diabetic retinopathy, *ETDRS* Early Treatment Diabetic Retinopathy Study, *HbA1c* glycosylated hemoglobin, *NPDR* nonproliferative diabetic retinopathy, *PDR* proliferative diabetic retinopathy, *SD* standard deviation, *VEGF* vascular endothelial growth factor

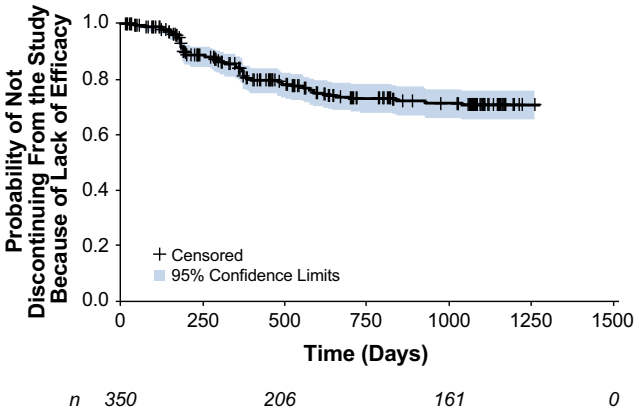

Fig. 1 Kaplan–Meier analysis of time to patient discontinuation from the study because of lack of efficacy. At the end of follow-up, the estimated probability of discontinuing from the study because of lack of efficacy was 29%

the second and the third year of the study (Fig. 2a). However, this increase resulted from patient selection rather than from continued improvement in BCVA, because almost half of the sham-treated patients had discontinued from the study by month 15, and BCVA outcomes on average were poorer in patients who discontinued from the study than in patients who completed the study (Fig. 2b). The mean (± SD) change in BCVA from baseline in sham-treated patients using last available postbaseline data (usually collected at the month 36/39 or early exit visit) was + 4.8 ± 13.0 letters (range − 57 to + 30, $n = 152$) in patients who completed the study and − 2.8 ± 13.5 letters (range − 66 to + 29, $n = 188$) in patients who exited the study early. The mean (± SD) change in BCVA from baseline among all sham-treated patients at their last visit with available data was + 0.9 ± 13.2 letters ($n = 349$).

Favorable visual outcomes in some patients despite the lack of active treatment were also seen in the analysis of percentage of patients who had at least 15-letter BCVA gains from baseline. On average, patients in the sham group had at least 15-letter BCVA improvement from baseline at 9.7% of their follow-up visits (range 0 to 100%). The mean (standard error of the mean, SEM) average change in BCVA from baseline during the study in sham-treated patients, evaluated using the AUC approach, was 2.0 (0.43) letters [19].

Evaluation of the distribution of patients with gain, loss, or no change (< 5 letters) in BCVA from baseline showed that at each visit, < 20% of patients with available data had a loss in BCVA of 5 letters or more (Fig. 3). The percentage of patients with a > 10-letter gain in BCVA increased during the study period, consistent with the findings that on average, patients who exited the study early had poorer BCVA outcomes. At their last visit with available data (typically at month 36/39 or early exit, $n = 349$), 37.5% of patients had no change in BCVA from baseline, 14.3% had a 5–10-letter gain, 23.2% had a > 10-letter gain, 8.9% had a 5–10-letter loss, and 16.0% had a > 10-letter loss.

Table 2 Parameters in patients who exited the study early and patients who completed the study

Parameter, mean (SD)	Patients who exited the study early ($n = 198$)	Patients who completed the study ($n = 152$)
At baseline		
BCVA, letters	56.7 (8.75)	57.2 (8.66)
CRT, μm	476 (135)	442 (127)
At last available visit		
BCVA, letters	54.1 (14.3)	62.0 (14.5)
CRT, μm	458 (196)	308 (164)
Systolic blood pressure change from baseline, mm Hg	− 1.1 (17.9)	− 2.0 (16.5)
Diastolic blood pressure change from baseline, mm Hg	− 0.0 (12.1)	− 2.2 (10.3)
HbA1c change from baseline, %	0.1 (1.1)	0.3 (1.2)
GFR change from baseline, mL/min	− 8.0 (19.3)	− 9.7 (15.8)

BCVA best-corrected visual acuity, *CRT* central retinal thickness, *GFR* glomerular filtration rate, *HbA1c* glycosylated hemoglobin, *SD* standard deviation

Anatomic outcomes

Analysis of the mean change in CRT from baseline at scheduled visits suggested continual improvement in CRT through month 33 of the study, when the mean change in CRT from baseline was − 150 μm (Fig. 4). However, almost two thirds of patients had missing data at month 33, and the early exit of sham patients with less favorable anatomic improvement resulted in greater apparent improvement in CRT in the remaining patients at visits in the second and the third year of the study. The mean (± SD) change in CRT from baseline using last available postbaseline data was − 131 ± 173 μm in patients who completed the study (range − 783 to + 462, $n =$ 148) and − 12 ± 171 μm in patients who exited the study early (range − 479 to + 478, $n = 178$).

The percentage change in CRT from baseline was greater in patients with baseline CRT > 400 μm than in patients with baseline CRT ≤ 400 μm (Fig. 5). For patients with baseline CRT > 400 μm, mean CRT at baseline was 536 μm, and the mean (± SD) percentage change in CRT from baseline at patients' final postbaseline evaluation was − 20.1% ± 33.3% ($n = 196$). For patients with baseline CRT ≤ 400 μm, mean CRT at baseline was 328 μm, and the mean (± SD) percentage change in CRT from baseline at patients' final postbaseline evaluation was − 2.2% ± 45.3% ($n = 120$).

The percentage of patients with CRT < 300 μm in the study eye increased during the study period (figure in Online Resource 1). At their last visit with data available, CRT in the study eye was < 300 μm in 41.5% of patients.

The figure in Online Resource 2 shows the mean change in DR severity from baseline at follow-up evaluations. Among all patients with DR severity assessed and recorded, only 6.5% (16 of 248 patients) had at least a two-step increase in DR severity from baseline at their last visit with data available.

Factors predictive of outcomes

Table 3 shows the full model of factors associated with BCVA change from baseline at the last available visit. Age, hypertension, baseline DR severity score, and baseline BCVA were identified as significant prognostic factors in the final model after stepwise selection (Table 4). BCVA gain from baseline at the last visit was 5.8 letters worse in patients with a history of hypertension versus patients with no history of hypertension. Older patients also had less favorable BCVA outcomes: each 10-year increase in patient age was associated with 2.9 letters worse BCVA gain from baseline at the last visit. Less severe DR was associated with better improvement in BCVA: a DR severity score of ≤ 6 at baseline was associated with 4.3 letters greater BCVA gain at the last visit compared with a DR severity score of > 6. A 10-letter higher BCVA score at baseline was associated with 2.8 letters worse BCVA gain from baseline at the last visit, suggesting a possible ceiling effect.

The full model of factors associated with the average BCVA change from baseline during the study (AUC approach) is shown in Table 5. Similar to the final model for BCVA change from baseline at the last visit, the final model for average BCVA change from baseline identified age, baseline DR severity score, and baseline BCVA as significant prognostic factors (Table 6). Each 10-year increase in patient age was associated with 1.6 letters less average gain in BCVA during the study, a DR severity score ≤ 6 at baseline was associated with 3.2 letters greater average BCVA improvement during the study, and a 10-letter higher BCVA score at baseline was associated with 2.1 letters worse average improvement in BCVA during the study, again suggesting a possible ceiling effect.

Table 7 shows the full model for the change in CRT from baseline at the last available visit. Age, baseline GFR, baseline CRT, and number of antihypertensive medications used

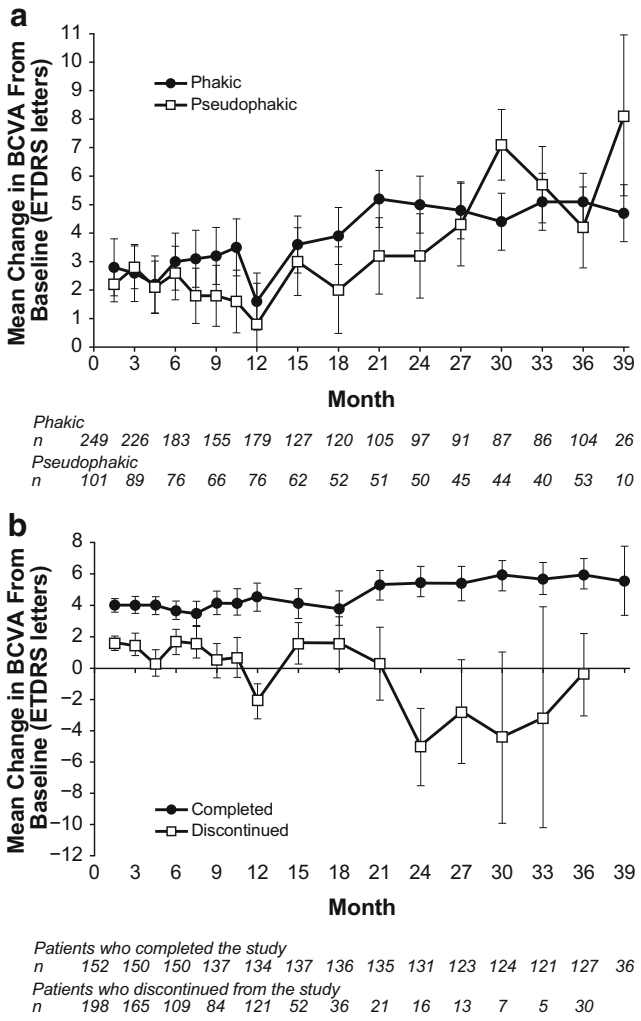

Fig. 2 Mean change in BCVA from baseline in the study eye of **a** sham-treated patients stratified by baseline lens status and **b** sham-treated patients stratified by study completion status. Mean baseline BCVA in study eyes was 56.9 letters (~20/70 Snellen equivalent) in all patients, 57.3 letters in baseline phakic patients, 56.0 letters in baseline pseudophakic patients, 57.2 letters in patients who completed the study, and 56.7 letters in patients who discontinued from the study. Analysis is based on observed values with no imputation for missing values. Error bars indicate the standard error of the mean. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

during the study period were identified as significant prognostic factors in the final model after stepwise selection (Table 8). Older patients had less improvement in CRT: each 10-year increase in patient age was associated with a 32-μm less reduction in CRT from baseline at the last visit. Higher baseline GFR also predicted less reduction in CRT from baseline at the last visit, with each 10 mL/min increase in baseline GFR associated with an 11-μm less reduction in CRT from baseline. Thicker baseline CRT predicted better reduction in CRT, with each 10-μm increase in CRT at baseline associated with a 4.6-μm greater reduction in CRT from baseline at the last visit. Use of antihypertensive medications during the study was also associated with better improvement in CRT: each additional medication used was associated with a 16-μm greater reduction in CRT from baseline at the last visit.

Discussion

The present analysis evaluated BCVA and CRT outcomes in sham-treated patients with DME followed for up to month 36/39 in the MEAD study. The results showed significant variability in the natural history of DME in these patients. At each visit during the first year of follow-up, patients were most likely to have no change in BCVA from baseline, but some patients had significant improvement in BCVA of more than 10 letters, and others had significant worsening in BCVA of more than 10 letters. Patients with poorer outcomes tended to exit the study early to receive rescue treatment. Baseline factors significantly associated with greater improvement in BCVA in the patients were younger age, lower DR severity score, and lower BCVA. The absence of a history of hypertension was also significantly associated with greater improvement in BCVA at the last available visit. With respect to anatomic outcomes, baseline factors associated with greater reduction in CRT from baseline were younger age, lower baseline GFR, and thicker CRT. Use of a larger number of antihypertensive medications during the study predicted better improvement in CRT.

Because of the availability of effective pharmacologic treatments for DME, we anticipate that there will not be opportunities in the future to study the natural history of DME and investigate relationships of systemic factors to improvement or worsening of DME in untreated patients. The sham group in the MEAD study, comprising patients who underwent sham procedures to maintain masking of patients and investigators, may be the last study population with DME that is followed for years without any active treatment, and that, therefore, could provide information regarding the natural history of DME. Changes in BCVA from baseline were similar in baseline phakic and pseudophakic eyes in these patients, suggesting that cataract development and surgery were not significant factors affecting BCVA outcomes. At their last visit with data available, 41.5% of patients had achieved CRT of < 300 μm and 23.2% of patients had achieved a > 10-letter gain in BCVA from baseline, suggesting that retinal edema may significantly improve or resolve spontaneously in some patients, with accompanying gains in visual acuity. However, the mean change in BCVA from baseline at the last available visit was only + 0.9 letters. These results reinforce the need for treatment to improve BCVA in patients with DME. Prompt treatment is recommended, because there was evidence in the RISE/RIDE registration studies of ranibizumab that delay in anti-VEGF treatment of DME may lead to worse outcomes [24].

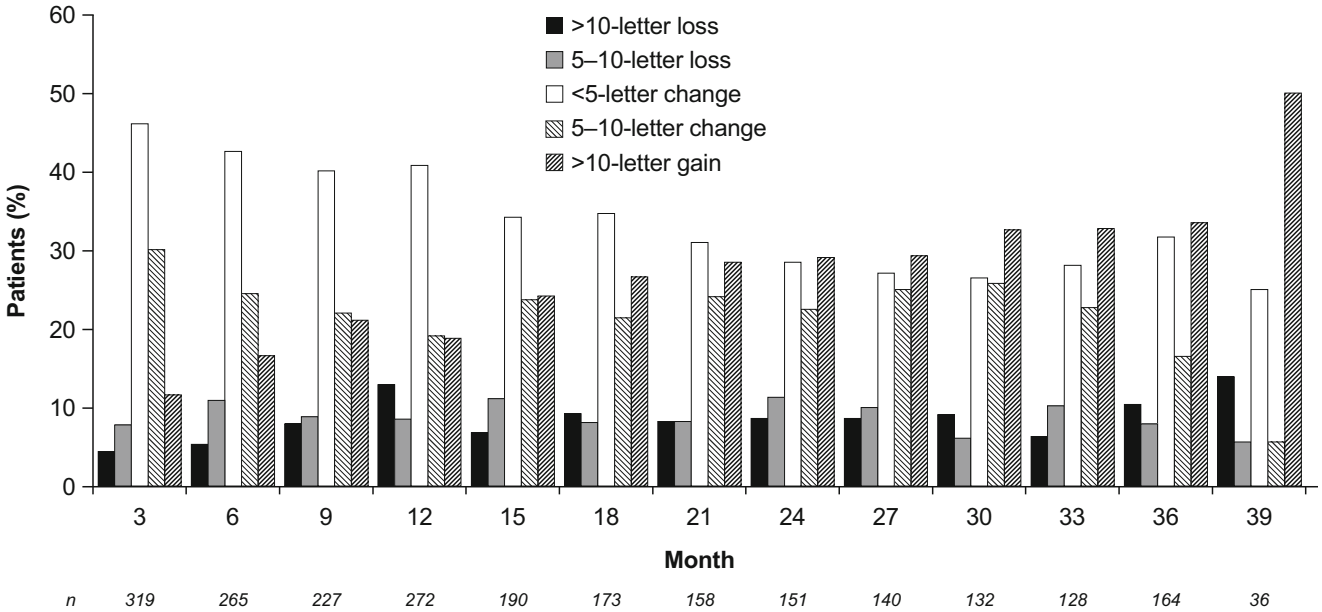

Fig. 3 Frequency distribution of the change in BCVA from baseline in the study eye of sham-treated patients. Analysis is based on observed values with no imputation for missing values. BCVA, best-corrected visual acuity

The requirement for patient discontinuation from the study before receiving rescue treatment influenced the mean changes in BCVA and CRT from baseline that were observed in the second and the third year of follow-up, because patients with poor outcomes frequently exited the study early. The missing data from these patients led to apparent improvements in visual and anatomic outcomes that did not reflect the natural history of DME in the total sham group, but instead reflect the natural history of DME in the subgroup of patients who did not discontinue from the study because of lack of efficacy or other reasons. To use data from as many patients in the sham group as possible, despite the high rate of discontinuations, the endpoints chosen for the models evaluating potential baseline and systemic factors associated with patient visual and anatomic outcomes were BCVA and CRT at the last visit with available data (rather than at month 36/39) and average change in BCVA from baseline across the study period.

Several studies have suggested a relationship between use of glitazones and the occurrence of DME [10, 11], but findings have been inconsistent, with a large longitudinal study reporting no significant association between glitazone use and the incidence of DME in type 2 diabetes patients [25]. In the MEAD study, the availability of repeated clinical assessments over a period of 3 years allowed the evaluation of potential risk factors for the improvement or aggravation of DME. A total of 55 (15.7%) patients in the sham group used a glitazone during the study period. Our analysis found no association

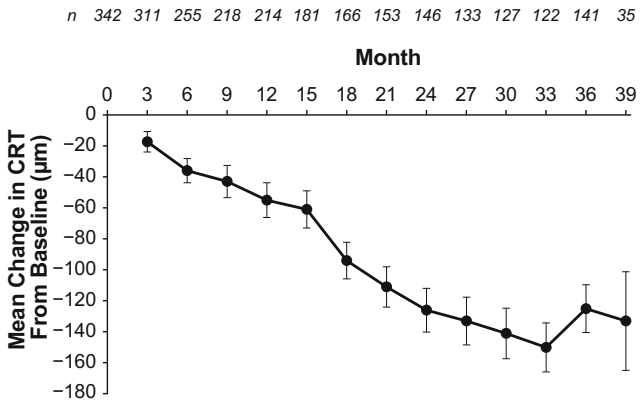

Fig. 4 Mean change in CRT from baseline in the study eye of sham-treated patients. Mean baseline CRT was 451 µm. Analysis is based on observed values with no imputation for missing values. Error bars indicate the standard error of the mean. CRT, central retinal thickness

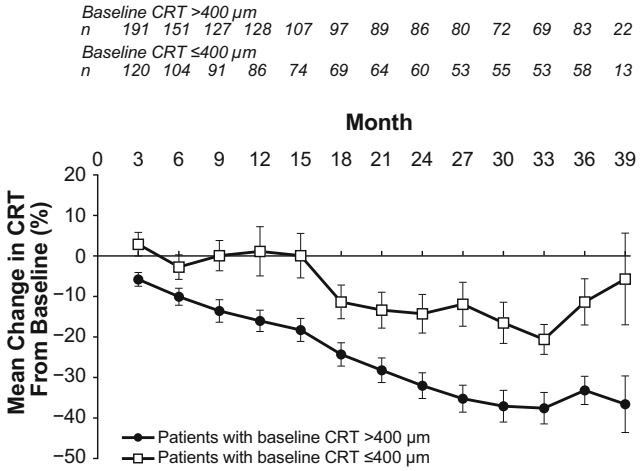

Fig. 5 Mean percentage change in CRT from baseline in the study eye of sham-treated patients stratified by baseline CRT. Analysis is based on observed values with no imputation for missing values. Error bars indicate the standard error of the mean. CRT, central retinal thickness

Table 3 Full model of predictors of BCVA change from baseline (letters) at the last available visit

Parameter	Estimate	Standard error	*P* value
Baseline patient characteristic			
Sex, female	1.007	1.559	0.519
Age, years	− 0.181	0.079	0.023
Race/ethnicity			
Caucasian	7.494	4.550	0.101
Black	8.833	5.456	0.107
Asian (not Japanese)	10.111	4.880	0.039
Hispanic	5.344	5.079	0.294
Japanese	− 5.222	14.087	0.711
BMI	0.013	0.131	0.922
HbA1c ≤ 8%	0.363	1.672	0.828
Systolic blood pressure, mm Hg	0.044	0.043	0.305
Diastolic blood pressure, mm Hg	0.087	0.073	0.235
Glomerular filtration rate, mL/min	0.043	0.030	0.151
History of hypertension	− 1.808	1.730	0.297
History of hypercholesterolemia	0.154	1.713	0.929
Duration of diabetes, years	0.000	0.085	0.996
Baseline study eye characteristic			
Phakic lens status	0.115	1.707	0.946
No prior DME treatment	− 2.517	1.721	0.145
DR severity score ≤ 6	2.468	1.557	0.114
BCVA	− 0.188	0.087	0.031
Duration of DME, months	0.023	0.027	0.390
During study period			
No concomitant use of platelet aggregation inhibitor	− 1.362	1.571	0.387
No concomitant use of glitazone	− 0.275	2.088	0.895
No concomitant use of medication to treat dyslipidemia	− 2.359	1.557	0.131
Number of antihypertensive medications used	0.257	0.611	0.674
Adverse event report(s) of dyslipidemia	3.169	3.253	0.331
Change in HbA1c from baseline at last visit	19.942	66.249	0.764

BCVA best-corrected visual acuity, *BMI* body mass index, *DME* diabetic macular edema, *DR* diabetic retinopathy, *HbA1c* glycosylated hemoglobin

between use of glitazones during the study and the average change in BCVA from baseline, or between use of glitazones during the study and the change in BCVA or CRT from baseline at the last available visit.

Table 4 Final model after stepwise selection of predictors of BCVA change from baseline (letters) at the last available visit

Parameter	Estimate	Standard error	*P* value
Baseline patient characteristic			
Age, years	− 0.289	0.095	0.003
History of hypertension	− 5.847	2.596	0.025
Baseline study eye characteristic			
DR severity score ≤ 6	4.312	1.849	0.021
BCVA	− 0.277	0.105	0.009

BCVA best-corrected visual acuity, *DR* diabetic retinopathy

It is well accepted that maintaining low HbA1c levels and near-normal blood pressure lowers the risk of the development and progression of DR [26]. However, there is a lack of evidence that interventions to reduce blood pressure are effective in reducing the risk of clinically significant DME [27]. In our analysis, history of hypertension was a significant factor predicting less improvement in BCVA at the last available visit, but was not significant in the model for average change in BCVA over the study period. Interestingly, the number of antihypertensive medications used during the study had a significant association with the reduction in CRT at the last available visit, suggesting that interventions to reduce blood pressure might be helpful in reducing retina edema.

There is evidence of a possible association between serum lipids and DME [4, 5], and studies have further suggested that use of lipid-lowering medications might reduce the incidence

Table 5 Full model of predictors of average BCVA change from baseline (letters, using the time-adjusted area-under-the-curve approach)

Parameter	Estimate	Standard error	*P* value
Baseline patient characteristic			
Sex, female	0.964	1.264	0.446
Age, years	−0.096	0.064	0.137
Race/ethnicity			
Caucasian	6.809	3.737	0.069
Black	8.481	4.484	0.060
Asian	8.394	4.003	0.037
Hispanic	3.915	4.144	0.346
Japanese	−5.662	11.577	0.625
BMI	−0.002	0.106	0.985
HbA1c ≤ 8%	0.145	1.352	0.915
Systolic blood pressure, mm Hg	0.018	0.035	0.612
Diastolic blood pressure, mm Hg	0.028	0.060	0.635
Glomerular filtration rate, mL/min	0.042	0.025	0.086
History of hypertension	−0.777	1.420	0.585
History of hypercholesterolemia	0.109	1.404	0.938
Duration of diabetes, years	−0.018	0.069	0.794
Baseline study eye characteristic			
Phakic lens status	−0.064	1.383	0.963
No prior DME treatment	−2.353	1.392	0.092
DR severity score ≤ 6	2.003	1.266	0.115
BCVA	−0.187	0.070	0.008
Duration of DME, months	0.021	0.022	0.350
During study period			
No concomitant use of platelet aggregation inhibitor	−0.826	1.272	0.517
No concomitant use of glitazone	−0.042	1.675	0.980
No concomitant use of medication to treat dyslipidemia	−2.195	1.263	0.083
Number of antihypertensive medications used	0.380	0.492	0.441
Adverse event report(s) of dyslipidemia	0.961	2.552	0.707
Change in HbA1c from baseline at last visit	62.884	53.103	0.237

BCVA best-corrected visual acuity, *BMI* body mass index, *DME* diabetic macular edema, *DR* diabetic retinopathy, *HbA1c* glycosylated hemoglobin

of DME [6, 28]. A study in 1011 patients with type 2 diabetes showed a relationship between lipid profiles and HbA1c levels [29]. Serum triglyceride levels were significantly higher and levels of high-density lipoprotein were significantly lower in patients with HbA1c ≤ 6% compared with patients with HbA1c > 6% [29]. Therefore, a possible confounding effect of hyperglycemia on serum lipids needs to be considered when evaluating the relationship between lipid profiles and DME. In our analysis, history of hypercholesterolemia, adverse event reports of dyslipidemia during the study, and use of medications to treat dyslipidemia during the study were not significant independent risk factors predicting BCVA or CRT outcomes. However, in the full model of average BCVA change (AUC approach), there was a trend for an association between use of medications to treat dyslipidemia and a 2.2-letter larger gain in BCVA ($P = 0.083$).

Table 6 Final model after stepwise selection of predictors of average BCVA change from baseline (letters, using the time-adjusted area-under-the-curve approach)

Parameter	Estimate	Standard error	*P* value
Baseline patient characteristic			
Age, years	−0.164	0.078	0.035
Baseline study eye characteristic			
DR severity score ≤ 6	3.164	1.515	0.038
BCVA	−0.210	0.086	0.015

BCVA best-corrected visual acuity, *DR* diabetic retinopathy

A recent study similar to the present study reported factors associated with BCVA and CRT outcomes at month 24 in patients treated with monthly sham injections in the RISE/RIDE trials [30]. Higher baseline BCVA, thinner

Table 7 Full model of predictors of CRT reduction from baseline (μm) at the last available visit

Parameter	Estimate	Standard error	*P* value
Baseline patient characteristic			
Sex, female	− 4.974	21.499	0.817
Age, years	− 0.649	1.098	0.555
Race/ethnicity[a]			
Caucasian	− 5.785	60.011	0.923
Black	− 37.333	73.357	0.611
Asian	77.405	64.668	0.232
Hispanic	− 43.613	68.438	0.525
BMI	0.835	1.805	0.644
HbA1c ≤ 8%	27.699	22.968	0.229
Systolic blood pressure, mm Hg	− 0.245	0.634	0.699
Diastolic blood pressure, mm Hg	0.556	1.052	0.598
Glomerular filtration rate, mL/min	− 0.855	0.404	0.035
No history of hypertension	− 25.851	23.990	0.282
No history of hypercholesterolemia	6.396	23.538	0.786
Duration of diabetes, years	− 0.278	1.178	0.814
Baseline study eye characteristic			
Phakic lens status	− 11.551	23.263	0.620
No prior DME treatment	− 19.447	23.704	0.413
DR severity score ≤ 6	− 32.081	20.977	0.127
CRT, μm	0.323	0.075	< 0.001
Duration of DME, months	0.072	0.362	0.843
During study period			
No concomitant use of platelet aggregation inhibitor	− 6.746	21.683	0.756
No concomitant use of glitazone	− 14.687	29.191	0.615
No concomitant use of medication to treat dyslipidemia	− 6.181	21.498	0.774
Number of antihypertensive medications used	14.306	8.034	0.076
No adverse event report(s) of dyslipidemia	− 48.901	44.497	0.273
Change in HbA1c from baseline at last visit	874.464	882.141	0.322

BMI body mass index, *CRT* central retinal thickness, *DME* diabetic macular edema, *DR* diabetic retinopathy, *HbA1c* glycosylated hemoglobin

[a] Japanese race (one patient) was not included in the model because the patient had missing CRT data

baseline CRT, absence of history of renal disease, and baseline presence of hard exudates in the center subfield were associated with good BCVA (20/40 or better) at month 24; younger age, lower baseline BCVA, and thinner baseline CRT were associated with achievement of a ≥ 15-letter gain in BCVA from baseline at month 24; lower baseline BCVA, absence of history of hypercholesterolemia, history of retinal disease, and presence of intraretinal cysts were associated with poor BCVA (20/100 or worse) at month 24; presence of intraretinal cysts, presence of subretinal fluid, and history of renal disease

Table 8 Final model after stepwise selection of predictors of CRT reduction from baseline (μm) at the last available visit

Parameter	Estimate	Standard error	*P* value
Baseline patient characteristic			
Age, years	− 3.240	1.201	0.008
Glomerular filtration rate, mL/min	− 1.098	0.442	0.014
Baseline study eye characteristic			
CRT, μm	0.456	0.083	< 0.001
During study period			
Number of antihypertensive medications used	16.212	7.809	0.039

CRT central retinal thickness

were associated with a ≥ 15-letter loss in BCVA from baseline at month 24; and lower baseline BCVA, thinner baseline CRT, and statin use were associated with resolution of edema (CRT ≤ 250 μm) at month 24 [30]. The study population in RISE/RIDE [16] appeared similar in baseline characteristics to the study population in MEAD [19]; however, laser rescue treatment was allowed in RISE/RIDE, and sham-treated patients received a mean of 1.6 (RIDE) or 8.8 (RISE) laser treatments (range 0–7) between study baseline and month 24 [16]. The extent to which laser treatments may have affected outcomes and the identification of prognostic factors for outcomes in the sham group of RISE/RIDE is unknown.

Consistent with the report from the RISE/RIDE studies, our analysis identified older age as a significant factor associated with worse improvement in BCVA from baseline across the follow-up period and at the last visit with available data. Consistent with these findings, older age was also associated with worse improvement in CRT from baseline at the last visit with available data.

Our evaluation of factors associated with outcomes in sham-treated patients with DME in the MEAD study had several limitations. Because of the limited size of the study population and the patient selection criteria used in the MEAD study, not all factors that have been reported to be risk factors for DME, or that are likely to exacerbate DME, could be investigated. For example, pregnancy is a potential risk factor for DME [7], but women who were pregnant or could potentially become pregnant were excluded from MEAD. In addition, both obstructive sleep apnea [7] and anemia [31] have been reported to be risk factors for DME, yet the numbers of patients with sleep apnea and anemia in the sham group in the MEAD study were too small for meaningful analysis. The number of patients with vitreomacular adhesion similarly was too small for meaningful analysis. Laboratory data on serum lipid profiles were not collected, so any association between lipid profiles and exacerbation of DME could not be investigated. Finally, patients with HbA1c > 10% or GFR < 50 mL/min were excluded from the study, and patients in the study were monitored frequently and were encouraged to control their diabetes. This likely limited our ability to detect the influence of glycemic control and nephropathy on outcomes. Our findings are applicable to patients with characteristics similar to those of the patients who participated in the MEAD study, i.e., patients with center-involved DME who do not have uncontrolled diabetes, uncontrolled other systemic disease, or active retinal neovascularization.

Because many patients with poor outcomes exited the study early, it is difficult to draw conclusions regarding the overall vision of the untreated sham-control group. The last available data for patients showed a mean change in BCVA from baseline of + 0.9 letters, with 37.5% of patients having no change in BCVA from baseline. Furthermore, visual outcomes in this group may not reflect the natural history of DME in a broader patient population, because glycemic control is likely to be improved in patients enrolled in a clinical trial. With the advent of anti-VEGF therapies and long-acting dexamethasone implants, the vision of diabetics with central macular edema has significantly improved. The sham-treated group in the MEAD study has shown the importance of hypertension, renal disease, and starting vision and CRT as markers for progression. Older age and baseline DR score > 6 were identified as significant risk factors for worse average change in BCVA across the study period. Thicker baseline CRT and a larger number of antihypertensive medications used were significant factors associated with better improvement in CRT during the study period.

Acknowledgments Writing and editorial assistance was provided to the authors by Kate Ivins, PhD, of Evidence Scientific Solutions, Philadelphia, PA, and funded by Allergan plc. All authors met the ICMJE authorship criteria. Neither honoraria nor payments were made for authorship.

Funding information This study was sponsored by Allergan plc, Dublin, Ireland. Y.H. Yoon, D.S. Boyer, R.K. Maturi, F. Bandello, and R. Belfort Jr. are consultants to Allergan. A.J. Augustin has received research support and speaker fees from Allergan. X.-Y. Li, Z. Bai, and Y. Hashad are employees of Allergan. The authors have full control of all primary data and they agree to allow *Graefe's Archive for Clinical and Experimental Ophthalmology* to review their data upon request.

Compliance with ethical standards

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

Appendix 1

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Appendix 2

I. Platelet aggregation inhibitors (includes acetic acid derivatives and related substances, aminosalicylic acid and similar agents, anilides, anti-inflammatory and antirheumatic agents; heparin and similar agents; nonsteroidal anti-inflammatory agents and preparations, other anti-inflammatory and antirheumatic agents, platelet aggregation inhibitors excluding heparin, proprionic acid derivatives, and salicylic acid and derivatives)

Abciximab; aceclofenac; acetametacin; acetylsalicylate lysine; acetylsalicyclic acid; Algiril; Arthrotec; Asasantin; Ascriptin; aspirin; Axotal; bromefenac sodium; Bufferin; certoparin sodium; cilostazol; clopidogrel; clopidogrel bisulfate; Co-Advil; Couldina; dalteparin sodium; dexibuprofen; dexketoprofen trometamol; diclofenac; diclofenac diethylamine; diclofenac potassium; diclofenac sodium; dicolfenac; dicolfenac sodium; dipyridamole; Dolmina; Doppel-Splat; enoxaparin; enoxaparin sodium; eptifibatide; etodolac; Flukit; flurbiprofen; flurbiprofin sodium; glucosamine; glucosamine sulfate; glucosamine w/chondroitin sulfate; heparin; heparin beraprost sodium; heparin calcium; heparin sodium; Ibupain; ibuprofen; ibuprofen arginine; ibuprofen w/paracetamol; Ilvico N; indobufen; indometacin; ketoprofen; ketorolac; ketorolac tromethamine; lonazolac; lonazolac calcium; loxoprofen; loxoprofen sodium; mesalazine; morniflumate; nabumetone; nadroparin; nadroparin

calcium; naproxen; naproxen sodium; Nefazan Compuesto; nepafenac; niflumic acid; nimesulide; pantoprazole sodium; Paynocil; prosugrel hydrochloride; salicylates NOS; sarpogrelate; sarpogrelate hydrochloride; sesquihydrate; sulfasalazine; sulodexide; talniflumate; Thomapyrin N; ticlopidine; ticlopidine hydrochloride; triflusal; zaltoprofen

II. Glitazones.
Pioglitazone; pioglitazone hydrochloride; rosiglitazone, rosiglitazone maleate

III. Medications used to treat dyslipidemia (includes bile acid sequestrants, fibrates, HMG CoA reductase inhibitors and combinations, combinations of lipid modifying agents, nicotinic acid derivatives, and other lipid modifying agents)

Atchol-Asp; atorvastatin; atorvastatin calcium; Caduet; colesevelam hydrochloride; colestyramine; bezafibrate; Ecosprin Av; Epacaps; ezetimibe; gamolenic acid; fenofibrate; fish oil; fluvastatin; fluvastatin sodium; gemfibrozil; Lorlip; lovastatin; HMG CoA reductase inhibitors, other combinati; HMG CoA reduct. inhib. in comb. with oth. lipid m; inegy; inositol nicotinate; lipid modifying agents, combinations; nicametate dihydrogen citrate; nicotinic acid; omega-3 fatty acids; omega-3 triglycerides; omega-3-acid ethyl ester; pitavastatin; pitavastatin calcium; policosanol; pravastatin; pravastatin sodium; rosuvastatin; rosuvastatin calcium; simvastatin; Zetitor

IV. Antihypertensive medications (includes ACE inhibitors, ACE inhibitors with calcium channel blockers, ACE inhibitors with diuretics, aldosterone antagonists, alpha-adrenoreceptor antagonists, selective and nonselective beta blocking agents, mixed alpha and beta blocking agents, beta blocking agents with diuretics, thiazides, or other antihypertensive agents, angiotensin II antagonists, angiotensin II antagonists with calcium channel blockers or in other combinations, benzothiazepine derivatives, calcium channel blockers with diuretics, dihydropyridine derivatives, diuretics, enzymes, ergot alkaloids, high-ceiling diuretics and potassium-sparing agent, low-ceiling diuretics and potassium-sparing agents; hydrazinophthalazine derivatives, imidazoline receptor agonists; imidazoline receptor agonists in combination with diuretics, methyldopa, nicotinic acid and derivatives, nitroferricyanide derivatives, other peripheral vasodilators, other potassium-sparing agents, phenylalkylamine derivatives, purine derivatives, rauwolfia alkaloids, renin-inhibitors, and thiazides)

ACE inhibitors; acebutolol; acebutolol hydrochloride; acetazolamide; Aldactazine; aldosterone antagonists; alfuzosin hydrochloride; aliskiren fumarate; amiloride; amlodipine; amlodipine besilate; amlodipine besylate w/ benazepril hydrochloride; amlodipine maleate; amlodipine w/ hydrochlorothiazide; amlodipine w/ valsartan; Amlong-A; angiotensin II antagonists and calcium channel blocker; angiotensin II antagonists and diuretics; Arkamin-H; atenolol; Azor; barnidipine hydrochloride; benazepril; bencyclane fumarate; bendroflumethiazide; Benicar HCT; benazepril hydrochloride; beta blocking agents and other diuretics; betaxolol hydrochloride; Bi Predonium; bisoprolol; bisoprolol fumarate; Blopress Plus; buflomedil; candesartan; candesartan cilexetil; captopril; carvedilol; celiprolol hydrochloride; Cibadrex; cilazapril; cilnidipine; cilostazol; clonidine; clonidine hydrochloride; Co-Betaloc; Co-diovan; delapril; diltiazem, diltiazem hydrochloride, Diovan Amlo; doxazosin; diuretics; doxazosin mesilate; Dyazide; Dynorm Plus; efonidipine; efonidipine hydrochloride; enalapril; enalapril maleate; enalapril maleate w/olercanidipin HCl; enalaprilat; eprosartan mesilate; felodipine; Fixocard; fosinopril; fosinopril sodium; Gezor; guanfacine; hydralazine; hydralazine hydrochloride; hydrochlorothiazide; hydrochlorothiazide w/ losartan; Hyzaar; indapamide w/perindopril; inositol nicotinate; irbesartan; isradipine; kallidinogenase; Karvea HCT; labetalol; labetalol hydrochloride; lacidipine; lercanidipine; lercanidipine hydrochloride; lininopril; lisinopril dihydrate; Loram-H; losartan; losartan potassium; Lotar; manidipine hydrochloride; Met XL AM; methyclothiazide; methyldopa; metoprolol; metoprolol fumarate; metoprolol succinate; metoprolol tartrate; Moduretic; moxonidine; nadolol; naftidrofuryl oxalate; nebivolol hydrochloride; nicametate dihydrogen citrate; nicardipine; nicardipine hydrochloride; nicergoline; nicotinic acid; nifedipine; nimodipine; nitrendipine; nitroprusside sodium; olmesartan; olmesartan medoxomil; pentoxifylline; perindopril; perindopril arginine; perindopril erbumine; potassium canrenoate; prazosin; prazosin hydrochloride; PritorPlus; propranolol; propranolol hydrochloride; quinapril; quinapril hydrochloride; ramipril; raubasine; reserpine; rilmenidine; rilmenidine phosphate; telmisartan; Telsar-A O; theoesberiven; trandolapril; zofenopril calcium; Salutec; Seloken Comp; serrapeptase; sotalol; Spilactone-T; spironolactone; tamsulosin; tamsulosin hydrochloride; Tenoretic; Teram; terazosin; terazosin hydrochloride; Twynsta; Unimax; urapidil; valsartan; Vascoride; Vaseretic; verapamil; verapamil hydrochloride; vinburnine; xantinol nicotinate; Zestoretic

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