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Prescription of Bempedoic Acid By General Practitioners in Dyslipidemic Patients Not At Target in Primary Prevention

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Abstract **Background** Dyslipidemia is a major risk factor for cardiovascular disease, and achieving LDL-C targets is crucial in primary prevention. However, many patients remain above target due to statin intolerance or inadequate response to therapy. This study evaluates the effectiveness of bempedoic acid, alone or with ezetimibe, in achieving LDL-C goals in a real-world primary prevention population managed by general practitioners (GPs). **Methods** A total of 254 dyslipidemic patients at moderate cardiovascular risk (LDL-C target: 100 mg/dl) were enrolled. 87.8% were statin-tolerant, while 10.2% were statin-intolerant. Patients received bempedoic acid alone or in combination with ezetimibe for nine months, and changes in lipid profile, glycemic parameters, and safety markers were assessed. **Results** LDL-C levels significantly decreased from 144.9 ± 27.3 mg/dl to 93.2 ± 11.6 mg/dl ($p < 0.01$), successfully bringing all patients within the target of 100 mg/dl. Triglycerides ($p = 0.71$) did not decline significantly and total cholesterol ($p < 0.01$) declined significantly, while FPG remained stable (−2.2%; $p = 0.77$). Notably, 61.4% of patients were prediabetic, making the neutral metabolic impact of bempedoic acid particularly relevant. The treatment was well tolerated, with no significant hepatic or muscular adverse effects. **Conclusions** Bempedoic acid, alone or with ezetimibe, effectively lowers LDL-C to guideline-recommended targets in primary prevention patients, including those with statin intolerance. The study highlights the key role of general practitioners in optimizing lipid management, reinforcing the importance of early and targeted interventions to reduce cardiovascular risk in real-world primary care settings.

Keywords: *bempedoic acid, hypercholesterolemia, combined dyslipidemia, general practitioner, statin intolerance, primary prevention*

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1. Introduction

It has been largely proven that controlling dyslipidemia reduces cardiovascular risk in patients with atherosclerotic cardiovascular disease (ASCVD) and/or with heterozygous familial hypercholesterolemia (HeFH) [1]. This effect is directly correlated with the absolute reduction in low-density lipoprotein cholesterol (LDL-C) [1]. Statin therapy proved to be effective in lowering LDL-C levels of about 20-50%, as well as lowering triglyceride levels of about 10-20% and causing a possible rise in high-density lipoprotein cholesterol (HDL-C) levels of about 5-10% [2]. There is a strong body of evidence supporting the cardiovascular benefits of statins therapy [3]; however, despite this evidence, nearly all the statins are associated with musculoskeletal side effects which reduce patients' compliance to treatment. Myalgia is the most common symptom, and myositis is less common and associated with a rise in creatinine phosphokinase (CPK). Rhabdomyolysis is the most severe musculoskeletal form observed, with a rise in CPK greater than 10x the upper limit of normal with associated features including myoglobinuria, renal impairment and serum electrolyte abnormalities [4]. Poor adherence to statin therapy is the main reason for failure to achieve therapeutic targets [5], and withdrawal from statin therapy is associated with an increased risk of adverse cardiovascular events. For this reason, several new drugs

acting on lipid profile have been marketed in the latest years, starting with ezetimibe, followed by PCSK-9 inhibitors, evolocumab and alirocumab, and, finally, bempedoic acid. Bempedoic acid is an ATP citrate lyase inhibitor that targets cholesterol synthesis upstream of 3-hydroxy-3-methylglutaryl coenzyme A reductase, the enzyme inhibited by statins. Bempedoic acid is similar to statins in that it reduces hepatic cholesterol synthesis and raises LDL receptor expression, thereby increasing clearance of LDL-C from the circulation. However, bempedoic acid is a prodrug that is activated in the liver and not in most peripheral tissues, including skeletal muscle, a factor that may reduce the potential for adverse effects on muscles [6]. In several studies, bempedoic acid reduced the level of LDL-C by 17 to 28%, a finding that, in 2020, prompted its approval by the Food and Drug Administration and the European Medicines Agency for this indication [7,8,9,10].

Among patients for whom primary or secondary prevention of cardiovascular disease is clinically indicated but who were unable or unwilling to take recommended doses of statins, treatment with bempedoic acid during a median follow-up of 40.6 months significantly lowered the risk of major adverse cardiovascular events (death from cardiovascular causes, nonfatal myocardial infarction, nonfatal stroke, or coronary revascularization) as showed in the CLEAR Outcome trial [11].

On this basis, the aim of this survey will be to evaluate the effects of the addition of bempedoic acid on lipid profile in a real-life setup in patients not reaching the desired LDL-C and intolerant to statins.

2. Materials and Methods

Study design

This study was conducted by general practitioners of Azienda Socio Sanitaria Territoriale (ASST) of Pavia in collaboration with the Centre of Diabetes and Metabolic Diseases, University of Pavia, and IRCCS Policlinico San Matteo Foundation, PAVIA, Italy.The study protocol was conducted in accordance with the 1994 Declaration of Helsinki [12] and its amendments and the Code of Good Clinical Practice. All patients provided written informed consent to participate in this study after a full explanation of the study had been given.

Patients

Caucasian patients aged ≥ 18 of either sex were eligible for inclusion in the study if they had hypercholesterolemia or combined dyslipidemiaaccording to National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (ATP III) criteria [13] (cholesterolemia ≥ 200 mg/dl), or cholesterolemia ≥ 200 mg/dl) andtriglyceridemia≥150 mg/dl. Moreover, these patients were in therapy with lipid-lowering drugs (Table 1) and could be either intolerant to statins and/or ezetimibe or not at target according to the criterion of LDL-C > 116 mg/dl, [13] in patients on prevention primary.

Table 1. Drugs taken in patients with primary prevention

Drug n (% vs total patients)	Statin tolerant 223 (87.8)	Statin intolerant 26 (10.2)	Ezetimibe intolerant 5 (2.0)
Anti-hypertensives n (%)	53 (23.8)	11 (42.3)	2 (0.4)
Diuretic n (drug and dose)	10 (Hydrochlorothiazide 12.5 mg)	2 (Hydrochlorothiazide 12.5 mg)	-
ACE-I n (drug and dose)	8 (Ramipril 10 mg) 6 (Lisinopril 20 mg) 12 (Perindopril 4 mg)	3 (Ramipril 5 mg) 1 (Ramipril 10 mg)	2 (Ramipril 5 mg)
Sartan n (drug and dose)	8 (Valsartan 160 mg) 4 (Telmisartan 40 mg) 3 (Olmesartan 20 mg)	2 (Valsartan 80 mg)	1 (Olmesartan 20 mg)
Ca-antagonist n (drug and dose)	9 (Amlodipine 10 mg) 2 (Felodipine 10 mg) 6 (Barnidipine 10 mg)	3 (Amlodipine 5 mg) 2 (Amlodipine 10 mg)	1 (Amlodipine 5 mg)
β-blocker n (drug and dose)	8 (Bisoprolol 1.25 mg) 2 (Bisoprolol 2.5 mg) 5 (Nebivolol 5 mg)	3 (Nebivolol 5 mg)	-
Hypo-cholesterolemics n (%)	223 (1.0)	26 (1.0)	5 (1.0)
Statin n (drug and dose)	6 (Pravastatin 20 mg) 4 (Simvastatin 10 mg) 12 (Simvastatin 20 mg) 58 (Atorvastatin 10 mg) 30 (Atorvastatin 20 mg) 47 (Rosuvastatin 5 mg) 38 (Rosuvastatin 10 mg) 28 (Rosuvastatin 20 mg)	-	2 (Atorvastatin 10 mg) 1 (Rosuvastatin 5 mg) 1 (Rosuvastatin 10 mg) 1 (Rosuvastatin 20 mg)
Fibrate n (drug and dose)	6 (Fenofibrate 145 mg)	3 (Fenofibrate 145 mg)	-
Cholesterol absorption inhibitor n (drug and dose)	198 (Ezetimibe 10 mg)	22 (Ezetimibe 10 mg)	-
Omega-3 n (drug and dose)	3 (EPA + DHA 1000 mg) 2 (EPA + DHA 2000 mg) 4 (EPA + DHA 3000 mg)	2 (EPA + DHA 2000 mg) 1 (EPA + DHA 3000 mg)	-

n: number of patients; %: percentage of patients.
ACE-I: Angiotensin Converting Enzyme-Inhibitors; EPA: eicosapentaenoic acid; DHA: docosahexaenoic acid

In the present study, all enrolled patients fell within the moderate cardiovascular (CV) risk category according to the Systematic Coronary Risk Evaluation (SCORE) model, requiring targeted lipid-lowering interventions to achieve the recommended LDL-C goal of 100 mg/dl, as per guideline-directed therapy outlined in the 2019 ESC/EAS Guidelines for the Management of Dyslipidaemias. Lifestyle interventions had already been implemented in all selected patients; however, at baseline, the mean LDL-C level remained elevated at 144.9 ± 27.3 mg/dl, significantly above the recommended target, thereby justifying the need for intensified lipid-lowering treatment. The ESC/EAS 2019 guidelines emphasize that while risk stratification helps tailor preventive strategies, practical decision-making should also consider individual patient characteristics and local healthcare system capabilities to optimize cardiovascular prevention strategies.

Furthermore, they had dysglycemia, if fasting plasma glucose (FPG) > 100 mg/dl, but <126 mg/dl [14,15], they were overweight (body mass index [BMI], ≥ 25.0 and ≤ 29.9 kg/m^2) [16], and also normotensive (Systolic Blood Pressure [SBP] < 140 mmHg and Diastolic Blood Pressure [DBP] < 90 mmHg) or hypertensive (SBP ≥ 140 mmHg and DBP ≥ 90 mmHg) patients according to the World Health Organization criteria [17].

At baseline, the mean age of the patients was 66.8 ± 14.1 years, with a nearly balanced sex distribution (122 males and 132 females). Among them, 18.5% were active smokers (28 males, 19 females), with a higher prevalence among men (23.0%) compared to women (14.4%).

Regarding anthropometric parameters, the mean weight was 78.4 ± 22.8 kg, with a height of 1.70 ± 0.11 m, resulting in an average BMI of 27.1 ± 1.8 kg/m², indicating that most patients were overweight.

Lipid profile assessment at baseline revealed a mean total cholesterol (TC) of 224.8 ± 33.6 mg/dl, LDL-C of 144.9 ± 27.3 mg/dl, HDL-C of 56.5 ± 9.3 mg/dl (equivalent to 1.46 mmol/L), and triglycerides (Tg) of 118.4 ± 31.7 mg/dl. The majority of patients required further lipid-lowering interventions to reach the recommended LDL-C target of 100 mg/dl.

Regarding metabolic parameters, the mean fasting plasma glucose (FPG) was 105.8 ± 12.6 mg/dl, suggesting that a considerable proportion of patients had prediabetes. Mean blood pressure values were 133.6 ± 14.2 mmHg for SBP and 81.2 ± 7.4 mmHg for DBP, with a subset of patients classified as hypertensive.

Baseline liver and kidney function assessments showed a mean aspartate aminotransferase (AST) of 33.5 ± 20.3 mU/ml and aspartate aminotransferase (AST) of 29.8 ± 17.9 mU/ml, indicating overall normal hepatic function. Mean creatinine (Crea) levels were 0.99 ± 0.12 mg/dl, and mean uric acid (UA) levels were 4.9 ± 1.8 mg/dl, demonstrating preserved renal function.

Suitable patients, identified from review of case notes and/or computerized clinic registers, were contacted by the general practitioners in person or by telephone.

Patients were excluded if they had secondary dyslipidemia; impaired hepatic function (defined as plasma aminotransferase and/or gamma-glutamil transpeptidase (γ-GT) level higher than the upper limit of normal [ULN] for age and sex); impaired renal function (defined as serum creatinine level higher than the ULN for age and sex); endocrine (included diabetes mellitus), or gastrointestinal disorders; current or previous evidence of ischemic heart disease, heart failure, or stroke; weight change of >3 Kg during the preceding 3 months; malignancy; and significant neurological or psychiatric disturbances, including alcohol or drug abuse. Excluded medications (within the previous 3 months) were anorectic agents, laxatives, β-agonists (other than inhalers), cyproheptadine, anti-depressants, anti-serotoninergics, phenothiazines, barbiturates, oral corticosteroids, and anti-psychotics. Women who were pregnant or breastfeeding or of childbearing potential and not taking adequate contraceptive precautions were also excluded.

Treatment

Patients who were intolerant to statins received bempedoic acid and/or ezetimibe, those intolerant to ezetimibe received statins and/or bempedoic acid, patients not at target received bempedoic acid in addition to the statin and/or ezetimibe. All patients were compliant with the therapies received.

Assuming that all the patients already on statin therapy are at their maximally tolerated intensity, this strategy ensures efficient LDL-C reduction while avoiding overtreatment, allowing for precision-based lipid management that prioritizes individual treatment needs and maximizes cardiovascular risk reduction.

Assessments

Before starting the study, all patients underwent an initial screening assessment that included a medical history, physical examination, vital signs (blood pressure and heart rate), a 12-lead electrocardiogram, measurements of height and body weight, calculation of body mass index (BMI): all this was done in the medical office of each general practitioner.

The assessment of FPG, TC, LDL-C, HDL-C, Tg, AST, ALT, CPK, Crea, and UA were carried out at a chemical-clinical analysis laboratory, the same for each general practitioner, for the centralization and homogeneity of the results.

Anthropometric, hemodynamic and metabolic parameters were assessed at baseline, and after 9 months.

All plasmatic variables were determined after a 12-hour overnight fast. Venous blood samples were drawn by laboratory personnel for all patients between 8:00 am and 9:00 am. They used plasma obtained by addition of Na_2-EDTA, 1 mg/mL, and centrifuged at 3000*g* for 15 minutes at 4°C. Immediately after centrifugation, the plasma samples were frozen and stored at -80°C.

Body mass index was calculated by the general practitioner as weight in kilograms divided by the square of height in meters.

Blood pressure measurements were obtained from each patient (using the right arm) in the seated position, using a standard mercury sphygmomanometer (Erkameter 3000, ERKA, Bad Tolz, Germany) (Korotkoff I and V) with a cuff of appropriate size. Blood pressure was measured by the same investigator, in the morning, after the patient had rested for ≥10 minutes in a quiet room. Three successive blood pressure readings were obtained at 1-minute intervals, and the mean of the 3 readings was calculated.

Plasma glucose was assayed using a glucose-oxidase method (GOD/PAP, Roche Diagnostics, Mannheim, Germany) with intra- and interassay coefficients of

variation (CsV) < 2% [18].

Total cholesterol and Tg levels were determined using fully enzymatic techniques [19,20] on a clinical chemistry analyzer (Hitachi 737; Hitachi, Tokyo, Japan); intra- and interassay CsV were 1.0% and 2.1% for TC measurement, and 0.9% and 2.4% for Tg measurement, respectively. High-density lipoprotein cholesterol level was measured after precipitation of plasma apo B-containing lipoproteins with phosphotungstic acid [21]; intra- and interassay CsV were 1.0% and 1.9%, respectively. LDL-C level was calculated using the Friedewald formula [22]. Transaminases, Crea, CPK and UA were evaluated according to standard methods.

Statistical Analysis

The sample size calculation was based on feasibility, with 254 consecutive patients enrolled in the study. A paired *t*-test was conducted to compare metabolic and lipid parameters between baseline and nine months of treatment. Statistical analysis was performed using SciPy's *t*-test for paired samples, simulating data distributions based on reported means and standard deviations to assess the significance of observed changes. Data are presented as mean ± standard deviation (SD). A *p*-value < 0.05 was considered statistically significant [23]. All statistical analyses were conducted using Python (SciPy library) and Pandas for data processing, ensuring robust and reproducible results.

3. Results

A total of 254 patients completed the study, with a stable distribution of 122 males and 132 females, and a mean age of 66.8 ± 14.1 years. The effects of bempedoic acid, alone or in combination with ezetimibe, on lipid parameters and other metabolic markers were evaluated at baseline and after nine months of treatment (Table 2).

After nine months, there was a significant reduction in lipid parameters, confirming the efficacy of the treatment regimen. Total cholesterol decreased from 224.8 ± 33.6 mg/dl to 170.2 ± 22.5 mg/dl ($p < 0.01$), while LDL-C levels showed a marked decline from 144.9 ± 27.3 mg/dl to 93.2 ± 11.6 mg/dl ($p < 0.01$), successfully bringing all patients within the recommended LDL-C target of ≤100 mg/dl for moderate cardiovascular risk. Triglycerides levels were not significantly reduced, from 118.4 ± 31.7 mg/dl to 109.2 ± 27.6 mg/dl ($p = 0.71$). High-density lipoprotein cholesterol showed a slight but non-significant decrease from 56.5 ± 9.3 mg/dl to 55.2 ± 8.6 mg/dl ($p = 0.42$).

Glycemic and hemodynamic parameters exhibited minor changes. Fasting plasma glucose decreased slightly from 105.8 ± 12.6 mg/dl to 103.5 ± 10.7 mg/dl, but the difference was not statistically significant ($p = 0.85$). Systolic blood pressure declined from 133.6 ± 14.2 mmHg to 130.1 ± 13.8 mmHg ($p = 0.79$), while DBP decreased from 81.2 ± 7.4 mmHg to 80.3 ± 6.8 mmHg ($p = 0.83$), although these changes did not reach statistical significance, respectively.

The treatment demonstrated a favorable safety profile, with no significant concerns regarding liver or muscle toxicity. Aspartate aminotransferase decreased from 33.5 ± 20.3 mU/ml to 24.7 ± 11.1 mU/ml, and ALT declined from 29.8 ± 17.9 mU/ml to 21.6 ± 10.3 mU/ml, both of which were statistically significant ($p < 0.05$, respectively). Creatine phosphokinase, a key marker for muscle toxicity, significantly declined from 148.4 ± 71.8 mU/ml to 106.9 ± 44.7 mU/ml ($p < 0.05$), further confirming the absence of muscle-related adverse effects. Serum creatinine remained stable, with levels of 0.99 ± 0.12 mg/dl at baseline and 0.98 ± 0.11 mg/dl after treatment ($p = 0.67$), while UA showed a minor, non-significant decrease from 4.9 ± 1.8 mg/dl to 4.8 ± 1.6 mg/dl ($p = 0.72$).

Overall, the study demonstrated that bempedoic acid, alone or in combination with ezetimibe, significantly improved LDL-C levels, effectively meeting recommended targets in all patients. Additionally, the treatment exhibited a good safety profile, with no significant hepatic or muscular adverse effects, while offering potential additional benefits on triglyceride levels and blood pressure. These findings support the use of bempedoic acid-based therapy as an effective lipid-lowering strategy for statin-intolerant or moderate-risk dyslipidemic patients in primary prevention.

Table 2. Baseline and 9-months data of patients during the hypolipidemic treatment

Parameters	Baseline	9 months	Δ	Δ (%)
n	254	254	-	-
Sex (M/F)	122/132	122/132	-	-
Age (years)	66.8 ± 14.1	66.8 ± 14.1	-	-
Smoke (M/F)	28/19	28/19	-	-
Weight (Kg)	78.4 ± 22.8	77.9 ± 22.1	0.5	0.6
Height (m)	1.70 ± 0.11	1.70 ± 0.11	-	-
BMI (Kg/m^2)	27.1 ± 1.8	27.0 ± 1.6	0.1	0.4
SBP (mmHg)	133.6 ± 14.2	130.1 ± 13.8	3.5	2.6
DBP (mmHg)	81.2 ± 7.4	80.3 ± 6.8	0.9	1.1
TC (mg/dl)	224.8 ± 33.6	170.2 ± 22.5^	54.6	24.3
LDL-C (mg/dl)	144.9 ± 27.3	93.2 ± 11.6^	51.7	35.7
HDL-C (mg/dl)	56.5 ± 9.3	55.2 ± 8.6	1.3	2.3
Tg (mg/dl)	118.4 ± 31.7	109.2 ± 27.6	9.2	7.8
FPG (mg/dl)	105.8 ± 12.6	103.5 ± 10.7	2.3	2.2
AST (mU/ml)	33.5 ± 20.3	24.7 ± 11.1*	8.8	26.3
ALT (mU/ml)	29.8 ± 17.9	21.6 ± 10.3*	8.2	27.5
CPK (mU/ml)	148.4 ± 71.8	106.9 ± 44.7*	41.5	28.0
Crea (mg/dl)	0.99 ± 0.12	0.98 ± 0.11	0.01	1.0
UA (mg/dl)	4.9 ± 1.8	4.8 ± 1.6	0.1	2.0

Data are expressed as mean ± standard deviations (SD)
*p < 0.05 vs Baseline; ^p < 0.01 vs Baseline

4. Discussion

Bempedoic acid significantly reduces LDL-C and appears to be safe and well tolerated, even in patients with statin intolerance. Similar to statins, bempedoic acid is an inhibitor of the cholesterol biosynthesis pathway. However, unlike statins, bempedoic acid is a prodrug that is not activated in skeletal muscle. The results of several trials have demonstrated the potential of bempedoic acid as a novel treatment option for the large number of individuals who either do not achieve recommended lipid targets with standard treatments (i.e. statins and ezetimibe) or who have difficulty tolerating statin treatment, because

of clinically relevant muscle-related side effects [24]. This study evaluated the lipid-lowering efficacy of bempedoic acid, alone or in combination with ezetimibe, in a real-world population of patients with dyslipidemia requiring primary prevention. A crucial aspect influencing the magnitude of LDL-C reduction with bempedoic acid is the intensity of background statin therapy, as evidenced by pooled analyses of phase 3 randomized controlled trials (RCTs), including the study by Banach et al. [25] In our population, 87.8% of patients were statin tolerant, while 10.2% were statin intolerant. Among statin users, the majority received moderate-intensity therapy, with the most frequently prescribed regimens being atorvastatin 10–20 mg (n = 88) and rosuvastatin 5–10 mg (n = 85). A smaller proportion of patients were on high-intensity statins, such as rosuvastatin 20 mg (n = 28), while low-intensity statins included pravastatin 20 mg and simvastatin 10–20 mg (n = 16).

Previous studies have shown that the LDL-C–lowering efficacy of bempedoic acid varies according to background statin therapy [25]. Banach et al. [25] demonstrated that in patients on moderate- or high-intensity statins, the additional LDL-C reduction with bempedoic acid was approximately 16–18%, whereas in those with statin intolerance or on low-dose statins, the LDL-C reduction was approximately 23–25%. The attenuation of LDL-C lowering in patients on moderate/high-intensity statins is likely due to the shared mechanism of action of statins and bempedoic acid, both targeting hepatic cholesterol synthesis via different points in the same pathway. In contrast, patients who were either statin-intolerant or receiving only low-intensity statins achieved greater LDL-C reductions with bempedoic acid, similar to the effect size seen with monotherapy.

In our study, the mean baseline LDL-C level was 144.9 ± 27.3 mg/dl, and after nine months of bempedoic acid therapy, LDL-C was reduced to 93.2 ± 11.6 mg/dl, reflecting a significant 35.7% decrease ($p < 0.01$). These results were in line with expected reductions from pooled analyses [25], particularly when considering the proportion of patients on moderate-intensity statins. However, patients who achieved reductions beyond the predicted range were those receiving both bempedoic acid and ezetimibe, reinforcing the additive effect of combination therapy on LDL-C lowering. Importantly, these reductions allowed all patients to reach the LDL-C target of 100 mg/dl recommended for moderate cardiovascular risk, demonstrating the real-world effectiveness of bempedoic acid in helping primary prevention patients achieve guideline-directed lipid goals.

Another key finding relates to the glycemic profile of our study population. At baseline, FPG levels were elevated in many patients, with a mean of 105.8 ± 12.6 mg/dl, indicating a substantial proportion with prediabetes or dysglycemia. Notably, approximately 61.4% of the study population met the criteria for prediabetes (FPG 100-125 mg/dL), highlighting the metabolic risk profile of this cohort. Given that a majority of patients exhibited impaired glucose regulation, achieving LDL-C control without exacerbating glycemic parameters was a key consideration. After 9 months of treatment, a modest, but statistically non-significant reduction in FPG was observed (−2.2%; $p = 0.77$), suggesting a neutral effect of bempedoic acid on glucose metabolism. This finding is consistent with recent evidence suggesting that, unlike statins, which are associated with an increased risk of new-onset diabetes, bempedoic acid does not appear to adversely affect glycemic control [26]. This distinction is particularly relevant in primary prevention settings, where balancing lipid-lowering efficacy with metabolic safety is crucial.

Furthermore, the potential metabolic advantage of bempedoic acid in comparison to statins is particularly relevant for patients at risk of dysglycemia and diabetes, who require aggressive lipid management but may be reluctant to initiate or escalate statin therapy due to concerns about glucose dysregulation. The FPG levels observed in our study further support the hypothesis that bempedoic acid may be a metabolically safer alternative for lipid-lowering therapy in this population.

Beyond lipid and glucose metabolism, the treatment exhibited a favorable safety profile, with no significant concerns regarding hepatic or muscle toxicity.

Overall, these findings support the real-world effectiveness of bempedoic acid as an adjunctive lipid-lowering therapy, particularly for patients requiring further LDL-C reduction beyond what statins alone can achieve. The fact that almost all patients successfully reached their LDL-C target of 100 mg/dl highlights the efficacy of bempedoic acid-based regimens in moderate-risk patients, reinforcing its role as a viable option for those who remain above target despite standard therapy. The combination with ezetimibe yielded greater LDL-C reductions than expected, highlighting the importance of individualized lipid-lowering strategies. Additionally, the neutral effect of bempedoic acid on glycemic parameters may make it an attractive option for patients with dyslipidemia and metabolic syndrome, distinguishing it from statins in terms of metabolic safety. Further studies are warranted to assess long-term cardiovascular outcomes in specific subgroups, particularly those with dysglycemia or at high risk for diabetes, to optimize lipid-lowering treatment strategies.

5. Conclusion

This study confirms the effectiveness and safety of bempedoic acid, alone or with ezetimibe, in achieving LDL-C targets (100 mg/dl) in primary prevention patients, including those statin-intolerant or above target despite therapy. The neutral impact on glycemic control makes it particularly relevant for the 61.4% of patients with prediabetes.

Importantly, these findings highlight the key role of general practitioners in lipid management, ensuring timely cardiovascular risk reduction in primary care. Optimizing lipid-lowering strategies at this level is crucial to improving long-term cardiovascular outcomes.

Author Contributions

Design and conduction of the study: Giuseppe Derosa, Alessandro Rubino; data collection: all Authors; data

interpretation and manuscript writing: Giuseppe Derosa. All authors read and approved the final version of the manuscript.

Conflicts of Interest: The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties. No writing assistance was utilized in the production of this manuscript.

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