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Meta-analysis of the Safety and Efficacy of Bempedoic Acid

Low-density lipoprotein cholesterol (LDL-C) is a well-established modifiable cardiovascular risk factor. Therapeutic options such as statins, ezetimibe, or proprotein convertase subtilisin/kexin type-9 inhibitor that reduce LDL-C through upregulation of LDL receptors have shown to reduce the risk of cardiovascular events. A significant number of patients despite receiving high intensity statin therapy, or due to nonadherence or intolerance fail to achieve target goals for LDL-C reduction. Bempedoic acid is a recently approved lipid-lowering drug indicated for treatment of heterozygous familial hypercholesterolemia or established atherosclerotic cardiovascular disease as an adjunct to maximally tolerated statin therapy. Bempedoic acid is activated in the liver and reduces LDL-C through adenosine triphosphate-citrate lyase inhibition working up stream of the statin target 3-hydroxy-3-methylglutaryl-CoA reductase. Several clinical trials have demonstrated pharmacologic efficacy of bempedoic acid in LDL-C reduction.[1–9] However, none of these trials were powered to assess cardiovascular efficacy of bempedoic acid.[10,11] Moreover, while concerns exist that LDL-C-lowering therapies might potentiate the risk of diabetes mellitus (DM), safety of bempedoic acid with respect to DM and other adverse events remained uncertain. Herein, we present a meta-analysis to investigate the effects of bempedoic acid on clinical outcomes.

Eleven randomized controlled trials that enrolled patients with dyslipidemia, established or at risk of cardiovascular disease were selected using PubMed and Embase through 02/2020. Data were abstracted on baseline characteristics of patients (Table 1), and outcomes of interest (percent change in LDL-C, major adverse cardiac events, myocardial infarction, serious adverse events, muscle-related adverse events, nasopharyngitis, urinary tract infection, new/worsening DM, and gout). Risk of bias was assessed following the Cochrane bias risk assessment tool and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis.[12] The whole process of study search and selection and data abstraction were performed by 2 authors (MUK and MZK), independently. Outcomes were pooled using Mantel Haenszel random effect model. Categorical estimates were reported as risk ratio (RR) and continuous outcomes were calculated as mean difference with 95% confidence intervals (CIs). Heterogeneity was assessed by I^2 tests and publication bias using Egger's test. Statistical significance was set at 0.05. Comprehensive meta-analysis V-3.0 was used for all analyses.

Table 1
Baseline characteristics of participants and trials of bempedoic acid (180 mg) versus placebo

First author (year)	Phase	N	Age (years)	Baseline LDL-C (mg/dl)	Women	CHD	Hypertension	Diabetes	Statin	Ezetimibe	Follow-up (weeks)
Ballantyne (2013)	2	44	57.0	165.0	43.0 (%)	0	0	0	-	-	12
		44	56.0	167.0	30.0 (%)	0	0	0	-	-	
Gutierrez (2014)	3	30	55.3	125.2	43.3 (%)	-	26.7 (%)	100 (%)	-	-	4
		30	56.0	128.4	33.3 (%)	-	26.7 (%)	100 (%)	-	-	
Thompson (2015)	2/3	37	64.0	176.0	46.0 (%)	-	57.0 (%)	-	-	-	8
		19	60.0	185.0	58.0 (%)	-	53.0 (%)	-	-	-	
Thompson (2016)	2/3	100	59.0	166.0	51.0 (%)	0	-	-	-	-	12
		99	60.0	165.0	52.0 (%)	0	-	-	-	100 (%)	
Ballantyne (2016)	3	45	57.0	142.0	69.0 (%)	-	-	-	100 (%)	-	12
		45	56.0	131.0	49.0 (%)	-	-	-	100 (%)	-	
Ballantyne (2018)	3	181	63.8	129.8	60.2 (%)	-	61.3 (%)	19.3 (%)	32.6 (%)	100 (%)	12
		88	63.7	123.0	63.6 (%)	-	58.0 (%)	19.3 (%)	28.4 (%)	100 (%)	
Ballantyne (2019)	3	88	65.0	145.0	54.5 (%)	-	87.5 (%)	51.1 (%)	69.4 (%)	-	12
		41	65.4	141.0	41.5 (%)	-	85.4 (%)	41.5 (%)	65.8 (%)	-	
Ray (2019)	2/3	1488	65.8	103.6	26.1 (%)	97.4	78.9 (%)	28.6 (%)	99.8 (%)	7.8 (%)	52
		742	66.8	102.3	28.7 (%)	98	80.1 (%)	28.6 (%)	100 (%)	7.5 (%)	
Laufs (2019)	2/3	234	65.2	158.5	56.8 (%)	-	67.5 (%)	26.9 (%)	<10 (%)	-	24
		111	65.1	155.6	55.0 (%)	-	67.6 (%)	23.4 (%)	<10 (%)	-	
Lalwani (2019)	2	45	58.0	71.0	51.2 (%)	-	-	-	100 (%)	0	4
		23	58.0	86.0	43.5 (%)	-	-	-	100 (%)	0	
Goldberg (2019)	3	522	64.1	119.4	37.2 (%)	82.8	83.9 (%)	29.7 (%)	90.0 (%)	-	12
		257	64.7	122.4	34.6 (%)	79.8	87.2 (%)	31.5 (%)	89.0 (%)	-	

CHD = coronary heart disease; LDL-C = low-density lipoprotein cholesterol.

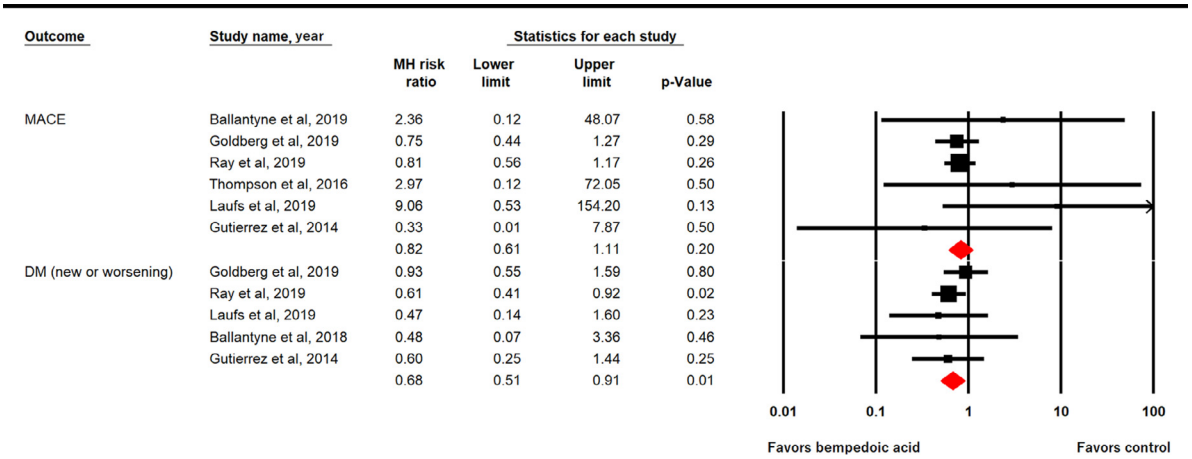

Figure 1. Forest plot comparing bempedoic acid versus control for major adverse cardiovascular events (MACE) and new or worsening DM (diabetes mellitus).

A total of 4,311 patients were included in this analysis. About 82% and 45% patients were on statin and ezetimibe therapy, respectively. The dose of bempedoic acid ranged from 60 to 180 mg/day. The median follow-up duration across the trials was 14 (4) weeks. The mean baseline LDL-C in study population was 136.7 (29.5) mg/dl, respectively. Bempedoic acid reduced the LDL-C by −14.08% [−14.39, −13.77, p <0.0001] compared with control. There were no significant differences between bempedoic acid and control with respect to risk of major adverse cardiac events (RR, 0.82; 95% CI 0.61 to 1.11; p = 0.20, $I^2 = 0$), myocardial infarction (RR, 0.60; 95% CI 0.35 to 1.04; p = 0.07, $I^2 = 0$), serious adverse events (RR, 1.06; 95% CI 0.89 to 1.26; p = 0.51, $I^2 = 0$), muscle-related adverse events (RR, 0.97; 95% CI 0.67 to 1.41; p = 0.87, $I^2 = 30.76$), urinary tract infection (RR, 0.80; 95% CI 0.55 to 1.32; p = 0.48, $I^2 = 24.13$), nasopharyngitis (RR, 0.89; 95% CI 0.71 to 1.12; p = 0.33, $I^2 = 0$), or gout (RR, 2.37; 95% CI 0.89 to 6.35; p = 0.09, $I^2 = 12.30$). However, bempedoic acid was associated with lower risk of new/worsening DM (RR, 0.68; 95% CI 0.51 to 0.91; p = 0.01, $I^2 = 0$) compared with control (Figure 1). Egger's test did not detect publication bias (p [2-tailed] = 0.76).

In this meta-analysis, we report that bempedoic acid significantly reduced the LDL-C levels compared with control. While, bempedoic acid did not reduce the risk of cardiovascular endpoints, the drug had a robust safety profile. Moreover, bempedoic acid was associated with prevention of new/worsening DM. The assessment of cardiovascular endpoints in most trials was underpowered, which most likely resulted in lack of cardiovascular benefits with bempedoic acid. Future powered trials with longer follow-up duration will provide more valuable insight into the role of bempedoic acid in reducing cardiovascular events. The benefit of using bempedoic acid for reducing risk of DM is an important observation, which was inconsistently appreciated in clinical trials. Bempedoic acid activates adenosine monophosphate activated protein kinase; the most likely mechanism of the drug for regulating carbohydrate metabolism.

This study has several limitations including low event rates, heterogeneity in study population, small sample size, short duration of follow-up, variation in dose, and combination therapy. The baseline population varied from low risk to high cardiovascular risk and we could not perform subgroup analysis due to lack of access to participant level data. The data on some key mortality and cardiovascular end points, such as stroke, were scarce.

In *conclusion*, bempedoic acid may be an effective and safe lipid-lowering therapy, with an additional protective role on DM. These results were demonstrated in the setting of ~82% patients taking statin therapy and ~45% taking ezetimibe therapy. The role of bempedoic acid as monotherapy needs further investigation. Overall, further randomized controlled trials are needed to assess the effects of bempedoic acid on cardiovascular endpoints and DM.

Disclosures

The authors have no conflicts of interest to disclose.

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Assessment of ST-Segment Elevation Myocardial Infarction Volume Trends During The COVID-19 Pandemic

Routine inpatient and outpatient health care has been greatly disrupted by the COVID-19 pandemic and both equipment and personnel have been redeployed in order to manage the crisis (https://www.cms.gov/newsroom/press-releases/cms-releases-recommendations-adult-elective-surgeries-non-essential-medical-surgical-and-dental). There have been anecdotal accounts (https://www.nytimes.com/2020/04/06/well/live/coronavirus-doctors-hospitals-emergency-care-heart-attack-stroke.html) and a publication [1] discussing the decrease in the number of ST-segment elevation myocardial infarction (STEMI) activiations. One explanation proposed for the decrease includes patients not seeking medical attention for ischemic symptoms due to fear of becoming infected by the coronavirus or presenting to the hospital late in their STEMI course.

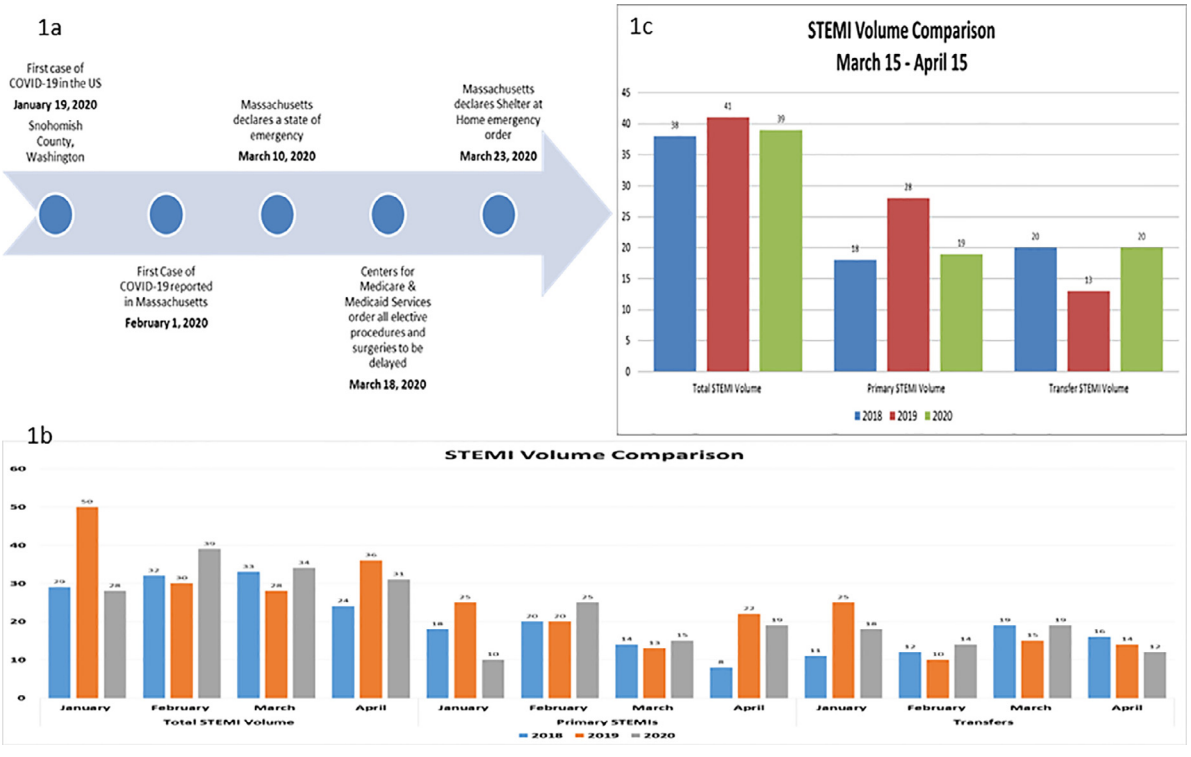

Figure 1. (1a) Timeline of the COVID-19 pandemic in the United States and Massachusetts. (1b) ST STEMI volume January through April 2020 compared to January through April 2018 and 2019. (1c) STEMI volume for March 15 through April 15, 2020 compared to March 15 through April 15, 2018 and 2019.