PARAMETER Study: LCZ696 Safe and Effective in Reducing Systolic and Pulse Pressure

Written by Alla Zarifyan

Bryan Williams, MD, University College London, London, United Kingdom, presented principal results of the PARAMETER study demonstrating that in older patients with systolic hypertension and arterial stiffness, the angiotensin receptor neprilysin inhibitor LCZ696 reduced central aortic systolic pressure (CASP) and central pulse pressure (CPP) more effectively than olmesartan, an angiotensin receptor blocker.

Hypertension in elderly patients is characterized by elevated systolic blood pressure (SBP) and increased CPP, which indicate large artery aging and stiffness and are predictive of cardiovascular disease and heart failure.

PARAMETER was a multicenter, randomized, double-blind, active-controlled, 52-week study designed to evaluate the safety and efficacy of LCZ696 on CASP and arterial stiffness in elderly patients with hypertension [Williams B et al. *BMJ Open*. 2014]. The patients were aged ≥60 years, with a SBP ≥150 mm Hg and pulse pressure (PP) >60 mm Hg.

A total of 454 patients were enrolled and randomized to LCZ696 200 mg daily (n=229) or olmesartan 20 mg daily (n=225) for 4 weeks, followed by a forced titration to double the initial doses for the next 8 weeks. The primary and the key secondary end points were evaluated at 12 weeks to determine the effect of LCZ696 400 mg daily vs olmesartan 40 mg daily on reducing CASP and CPP, respectively. Thereafter, patients with uncontrolled BP received add-on therapy as needed. Patients were followed for an additional 40 weeks after the initial evaluation, for a total follow-up period of 52 weeks.

At 12 weeks, the reduction in CASP was significantly higher with LCZ696 compared with olmesartan, at −12.6 mm Hg vs −8.9 mm Hg ($P=.01$). CPP was also reduced more significantly by LCZ696 compared with olmesartan, at −6.4 mm Hg vs −4.0 mm Hg ($P=.012$).

Brachial SBP at 12 weeks was lowered by 13.7 mm Hg vs 9.9 mm Hg with LCZ696 vs olmesartan, respectively ($P=.016$), while PP was lowered by 7.7 mm Hg vs 4.9 mm Hg ($P=.013$), respectively. LCZ696 also significantly lowered 24-hour brachial and central aortic SBP ($P<.001$ for both) compared with olmesartan, with the biggest difference between treatment groups occurring at night.

NT-proBNP, a marker for ventricular-vascular coupling, was lowered by 34% vs 20% with LCZ696 vs olmesartan, respectively.

At 52 weeks, CASP was lowered by 16.2 mm Hg with LCZ696 vs 14.7 mm Hg with olmesartan ($P=.27$), while CPP was lowered by 7.2 mm Hg vs 6.6 mm Hg ($P=.6$), respectively. Brachial SBP was lowered by 17.7 mm Hg vs 16.1 mm Hg with LCZ696 vs olmesartan, respectively ($P=.28$), while brachial PP was lowered by 8.8 mm Hg vs 8.0 mm Hg, respectively ($P=.48$).

Monotherapy was sufficient in 68% of patients treated with LCZ696 vs 53% of those treated with olmesartan. Both LCZ696 and olmesartan treatments were safe and well tolerated, and the key safety parameters (including any adverse events [AEs], serious AEs, or discontinuation due to AEs, serious AEs, drug-related AEs, or death) did not vary significantly between the groups.

Prof Williams summarized that the PARAMETER study met its primary and key secondary objectives and that LCZ696 provided beneficial effects on central aortic hemodynamics and function and can offer a therapeutic advantage beyond those observed with renin–angiotensin system blockade.

Extended DAPT Reduces Secondary Cardiovascular Events in Patients With Prior MI

Written by Alla Zarifyan

A meta-analysis of randomized controlled trials has demonstrated a substantial reduction in cardiovascular (CV) outcomes, including CV mortality, with dual antiplatelet therapy (DAPT) continued beyond 1 year vs aspirin alone, among patients with a prior myocardial infarction (MI) [Udell JA et al. *Eur Heart J*. 2015].

The recent trials examining the effect of extended DAPT in a variety of patient populations have produced heterogeneous results regarding its safety and efficacy, according to Jacob A. Udell, MD, MPH, University of Toronto, Toronto, Canada. He noted that in clinical practice DAPT is stopped at 1 year in about 50% of patients because of the lack of long-term data.

Dr Udell and colleagues conducted a systematic review and meta-analysis that evaluated whether long-term DAPT reduced CV risk when compared with aspirin alone in patients with a history of prior MI. The primary end point was a composite of major adverse CV events (MACEs) defined as CV death, MI, and stroke. The secondary end points included CV death, MI, stroke, non-CV death, all-cause mortality, major bleeding, and stent thrombosis.

The key features of the 6 trials included in the meta-analysis are shown in Table 1. The mean follow-up was 30 months, and there was a total of 2273 MACEs. The mean age of the patients was 64 years; 24% were women; and the mean time from MI was 18 months. Notably, few patients

Table 1. Trials Evaluated in Meta-analysis

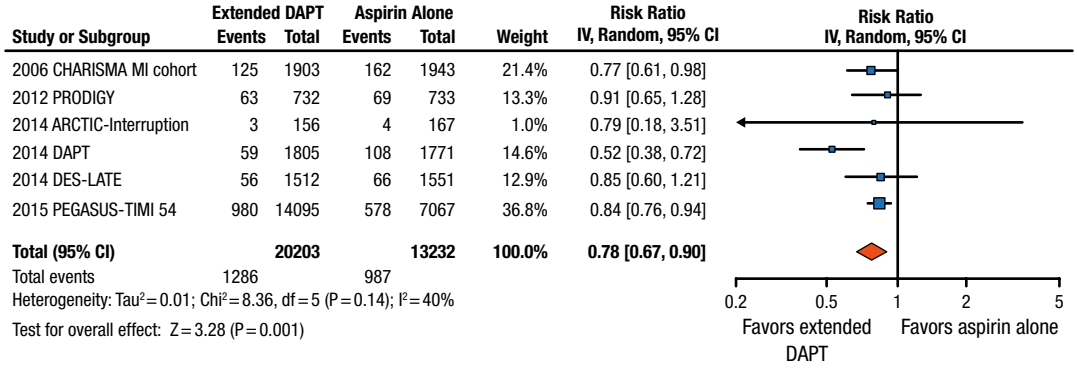
Trial	Subgroup/ Population	n	Drug	Duration, mo	No. of MACEs	Bleeding End Point
CHARISMA	Stable prior MI (mean, 24 mo)	3846	Clopi	28	287	GUSTO moderate/severe
PRODIGY	PCI for ACS	1465	Clopi	6 vs 24	132	TIMI major
ARCTIC-Interruption	PCI for ACS (excluded STEMI)	323	Clopi or pras	12 vs 24	7	STEEPLE major
DAPT	PCI for MI	3576	Clopi or pras	12 vs 30	167	GUSTO moderate/severe
DES-LATE	PCI for ACS	3063	Clopi	12 vs 24	122	TIMI major
PEGASUS TIMI-54	Stable prior MI (median, 20 mo)	21 162	Ticag	33	1558	TIMI major
Total		33 435		30	2273	

ACS, acute coronary syndromes; clopi, clopidogrel; DAPT, dual antiplatelet therapy; MACE, major adverse cardiovascular events; MI, myocardial infarction; mod, moderate; PCI, percutaneous coronary intervention; pras, prasugrel; STEMI, ST elevation myocardial infarction; ticag, ticagrelor.

Source: Udell JA et al. *Eur Heart J*. 2015.

Reproduced with permission from JA Udell, MD.

Figure1. Primary End Point: Major Adverse Cardiovascular Event



Risk of major adverse cardiovascular events comparing extended dual antiplatelet therapy vs. aspirin alone. Square data markers represent risk ratios and horizontal lines the 95% confidence intervals with marker size reflecting the statistical weight of the study using inverse variance random effects meta-analysis. A diamond data marker represents the overall risk ratios and 95% confidence intervals for major adverse cardiovascular events. There was no significant between-trial heterogeneity (Q statistic = 8.36, d.f. = 5; $P = 0.14$; $I^2 = 40\%$).

CV, cardiovascular; DAPT, dual antiplatelet therapy; MI, myocardial infarction.

Reprinted from Udell JA et al, Long-term dual antiplatelet therapy for secondary prevention of cardiovascular events in the subgroup of patients with previous myocardial infarction: a collaborative meta-analysis of randomized trials, *Eur Heart J*, 2015, by permission of Oxford University Press.

had unstable angina (7%), prior stroke or transient ischemic attack (3%), or prior coronary bypass surgery (7%).

The results for the primary end point showed a significant risk reduction of 22% with prolonged DAPT, with low heterogeneity across the trials. The rate of MACEs was 6.4% among the 20 203 patients assigned to DAPT vs 7.5% among the 13 232 patients receiving aspirin alone (RR, 0.78; $P = .001$; Figure 1). The rate of CV death alone was 2.3% for patients on DAPT vs 2.6% of those receiving aspirin (RR, 0.85; 95% CI, 0.74 to 0.98; $P = .03$). Prolonged DAPT also significantly reduced the risk of individual CV end points, such as MI (RR, 0.70; $P = .003$), stroke (RR, 0.81; $P = .02$), and stent thrombosis (RR, 0.50; $P = .02$).

The rate of major bleeding was significantly higher among patients receiving DAPT vs aspirin alone, at 1.9% vs 1.1%, respectively (RR, 1.73; $P = .004$). However, the rate of other bleeding events, such as intracranial hemorrhage (ICH), fatal bleeding, non-CV death, and all-cause death, was not significantly different between the treatment groups. All subgroup analyses demonstrated that extended DAPT was more effective than aspirin alone regardless of age, sex, DAPT regimen, index acute coronary syndrome, time from index MI, and history of percutaneous coronary intervention.

Dr Udell concluded that extending DAPT beyond 1 year decreased the risk of MACE, MI, stroke, and CV

death among high-risk patients with previous MI when compared with aspirin therapy alone. It also increased the risk of major bleeding but not fatal bleeding or ICH, and it did not increase the risk of death due to non-CV causes. However, he cautioned that prolonged DAPT is not appropriate for patients with anticoagulation issues, recent bleeding events or surgery, or history of ICH and that very few patients studied had prior stroke or a transient ischemic attack.

DAPT Study: Bleeding Increased but No Difference in Bleeding-Related Mortality

Written by Alla Zarifyan

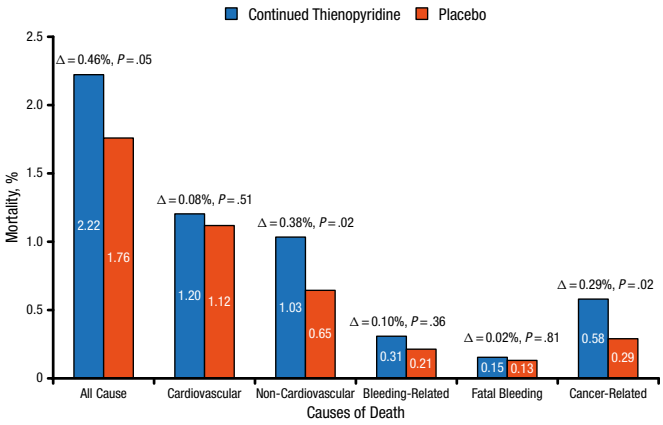
Prolonged dual antiplatelet therapy beyond 1 year was associated with increased mortality in the DAPT study, but whether this was related to the increased bleeding rates seen in the study was unknown [Mauri L et al. *N Engl J Med*. 2014]. A new analysis has revealed that cancer-related death accounted for the majority of the difference in mortality, and this appeared to be related to an imbalance in advanced cancers enrolled as there was no difference in cancer incidence, according to Laura Mauri, MD, Brigham and Women's Hospital, Boston, Massachusetts, USA.

The DAPT Study found that dual antiplatelet therapy with a thienopyridine plus aspirin beyond 1 year after coronary stenting, vs aspirin alone, reduced ischemic complications, but increased moderate or severe bleeding in patients treated with drug-eluting stents. The rates of major adverse cardiovascular and cerebrovascular events (MACCE; a composite of death, myocardial infarction [MI], and stroke) and MI were significantly lower in the continued thienopyridine group (n = 5020) compared with the placebo group (n = 4941), at 4.3% vs 5.9%, and 2.1% vs 4.1%, respectively (both $P < .001$); but the rate of all-cause death was higher in the continued thienopyridine group (2.0% vs 1.5%; $P = .05$).

The objective of the present analysis was to adjudicate and analyze deaths following randomization for all subjects (treated with either drug-eluting or bare metal stents), with particular focus on bleeding- and cancer-related outcomes. A total of 11 648 patients were randomized (5862 to continued thienopyridine vs 5786 to placebo).

There was a trend toward increased all-cause mortality for the 12- to 30-month period at 1.9% in the continued thienopyridine group vs 1.5% in the placebo group (HR, 1.31; 95% CI, 0.97 to 1.75; $P = .07$). It reached statistical significance for the 12- to 33-month period at 2.2% vs 1.8% (HR, 1.32; 95% CI, 1.00 to 1.73; $P = .05$). In the continued thienopyridine group, non-cardiovascular (CV) death was more

Figure 1. Mortality by Cause



12-33 months; n = 11 648 randomized.

Reproduced with permission from L Mauri, MD.

frequent during the 12- to 30-month period (0.9% vs 0.5%; HR, 1.94; 95% CI, 1.20 to 3.15; $P = .01$), whereas CV death was numerically more frequent during the 30- to 33-month period, as thienopyridine treatment was discontinued (0.3% vs 0.1%; HR, 2.39; 95% CI, 0.84 to 6.77; $P = .09$).

For the entire 12- to 33-month period, non-CV deaths and cancer-related deaths were significantly higher in the continued thienopyridine group compared with the placebo group, and the rate of bleeding-related deaths was very low and did not differ significantly between the groups (Figure 1). However, there was no difference in new cancer incidence after randomization. Most of these cancer-related deaths were solid tumors typical of such a population, rather than a particular location or cell type, and cancer deaths were rarely related to bleeding. Although life expectancy of less than 3 years was an exclusion criterion of the study, patients with cancer were allowed to be enrolled. These findings suggest that caution is warranted in choosing whether to continue long-term dual antiplatelet therapy in subjects with advanced cancer. There have been no observed increases in mortality [Elmariah S et al. *Lancet*. 2015] or cancer-related death [Hicks BM et al. *Pharmacoepidemiol Drug Saf*. 2015; Unger EF. *N Engl J Med*. 2009; Roe MT et al. *N Engl J Med*. 2012] across prior large randomized trials of thienopyridine therapy with extended follow-up.

Dr Mauri cautioned that there were several limitations to the study, including low event rates and the retrospective adjudication of cancer diagnosis. She concluded that dual antiplatelet therapy beyond 12 months after coronary stenting should be considered for the prevention of MI, but risks of continued dual antiplatelet therapy should be considered carefully.