

## BRIEF REPORT

# Effect of once-weekly dulaglutide versus insulin glargine in people with type 2 diabetes and different baseline glycaemic patterns: A post hoc analysis of the AWARD-2 clinical trial

Francesco Giorgino PhD<sup>1</sup>  | Maria Yu MS<sup>2</sup> | Axel Haupt MD<sup>2</sup>  |  
Zvonko Milicevic PhD<sup>2</sup>  | Luis-Emilio García-Pérez PhD<sup>2</sup> 

<sup>1</sup>Department of Emergency and Organ Transplantation, Section of Internal Medicine, Endocrinology, Andrology and Metabolic Diseases, University of Bari Aldo Moro, Bari, Italy

<sup>2</sup>Eli Lilly and Company, Indianapolis, Indiana

## Correspondence

Luis-Emilio García-Pérez, PhD, Global Medical Affairs Lilly S.A, Avenida de la Industria, 30, 28108 Alcobendas, Madrid, Spain.  
Email: [garcia\\_luis-emilio@lilly.com](mailto:garcia_luis-emilio@lilly.com)

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## Abstract

The long-acting glucagon-like peptide-1 receptor agonist dulaglutide acts by stimulating insulin secretion and reducing glucagon levels in a glucose-dependent manner both in the fasting and postprandial states, resulting in reductions of both fasting glucose (FG) and postprandial glucose (PPG). In contrast, the main mechanism of action of basal insulin is to reduce elevated FG by inhibiting hepatic glucose production. The aim of the present post hoc analysis of the phase 3 AWARD-2 trial was to investigate whether specific baseline glycaemic patterns respond differentially to dulaglutide compared to insulin glargine (glargine). We categorized participants into four subgroups based on prespecified glucose thresholds and their baseline FG and daily 2-hour mean PPG: low FG/low PPG; low FG/high PPG; high FG/low PPG; and high FG/high PPG. Changes in glycaemic measures in response to treatment with dulaglutide or glargine were evaluated in each subgroup. At 52 weeks, significant reductions from baseline in glycated haemoglobin (HbA1c) were observed in all subgroups with dulaglutide 1.5 mg and with glargine (all  $P < .05$ ), except in patients with low FG/low PPG who received glargine. Greater HbA1c reductions were observed with dulaglutide 1.5 mg compared to glargine in all subgroups (all  $P \leq .05$ ), except in the low FG/high PPG subgroup.

## KEYWORDS

basal insulin, dulaglutide, GLP-1, type 2 diabetes

## 1 | INTRODUCTION

Appropriate glucose control has to be achieved through reductions in both elevated fasting glucose (FG) and postprandial glucose (PPG), since both contribute to high glycated haemoglobin (HbA1c) levels and the development of complications in type 2 diabetes (T2D).<sup>1,2</sup> The long-acting insulin analogue, insulin glargine (glargine), exerts its action primarily through a decrease in hepatic

glucose production and consequent lowering of FG.<sup>3</sup> However, it has smaller effects on PPG and PPG excursions.<sup>4</sup> By contrast, once-weekly glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as dulaglutide, act by stimulating insulin secretion and reducing glucagon levels in both the fasting and postprandial states, thus reducing both FG and PPG levels. Additionally, GLP-1RAs contribute to a delay in gastric emptying, which has a role in further reducing PPG.<sup>5-7</sup> Due to the specific mechanism of action

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of insulin and GLP-1RAs, it is conceivable to expect differential responses to each treatment according to baseline glycaemic patterns. In the phase 3 Assessment of Weekly Administration of LY2189265 in Diabetes-2 (AWARD-2) trial, dulaglutide 1.5 mg demonstrated greater reductions in HbA1c with better weight control and less hypoglycaemia compared with glargine.<sup>8</sup>

The aim of the present non-prespecified post hoc analysis was to investigate the efficacy of dulaglutide versus glargine at 52 weeks in participants from the AWARD-2 trial with different glycaemic patterns. Specifically, drug-induced changes in HbA1c at different combinations of baseline values of FG and daily 2-hour mean PPG were examined, with a particular focus on participants who had predominantly high FG and low PPG levels and those who had predominantly low FG and high PPG levels.

## 2 | METHODS

### 2.1 | Study design

Participants ( $n = 766$ ) from the AWARD-2 clinical trial, which compared efficacy and safety of once-weekly dulaglutide with daily glargine, were included in this post hoc analysis. The AWARD-2 study design and results have been previously published.<sup>8</sup>

For this post hoc, non-prespecified analysis, participants treated with dulaglutide or glargine were categorized into the following subgroups, according to glucose levels, measured by self-monitored plasma glucose, at baseline: low FG/low PPG; low FG/high PPG; high FG/low PPG; and high FG/high PPG. The median baseline values of FG (8.4 mmol/L [151 mg/dL]) and PPG (10.1 mmol/L [182 mg/dL]) were used as thresholds to define subgroups and ensure an adequate number of participants in both the low FG/high PPG and high FG/low PPG groups, since the clinical thresholds for adequate glycaemic control (ie,  $<7.2$  mmol/L [130 mg/dL] for FG and  $<10.0$  mmol/L [180 mg/dL] for PPG)<sup>9</sup> would yield too small subgroups. The thresholds, therefore, for low FG and high FG and for low PPG and high PPG were based on the above median values. Baseline characteristics and changes at 52 weeks in glycaemic measures were analysed, including HbA1c, FG (FG – central laboratory values), PPG (self-monitored plasma glucose), and body weight. Additionally, rates of documented symptomatic hypoglycaemia with plasma glucose  $\leq 3.9$  mmol/L (70 mg/dL) and mean glargine doses were analysed.

### 2.2 | Statistical analyses

Analyses were performed on the intention-to-treat population and exclude efficacy endpoints post-rescue. Baseline characteristics were categorized by baseline FG and PPG. Outcome measures at 52 weeks were compared among baseline FG/PPG subgroups. Changes from baseline in glycaemic outcomes were analysed using analysis of

**TABLE 1** Baseline demographics and patient characteristics by subgroup

Variable	Low FG/low PPG, n = 292	Low FG/high PPG, n = 90	High FG/low PPG, n = 92	High FG/high PPG, n = 292	Overall, n = 766
Age, years	56.4 ± 10.0	56.3 ± 8.8	56.3 ± 9.5	56.8 ± 9.3	56.51 ± 9.5
Sex, male	141 (48.3)	53 (58.9)	51 (55.4)	150 (51.4)	395 (51.6)
Geographic region, n (%)					
Asia	45 (15.4)	23 (25.6)	12 (13.0)	31 (10.6)	111 (14.5)
Europe	112 (38.4)	30 (33.3)	35 (38.0)	121 (41.4)	298 (38.9)
Latin America	112 (38.4)	26 (28.9)	36 (39.1)	78 (26.7)	252 (32.9)
Other <sup>a</sup>	23 (7.8)	11 (12.2)	9 (9.8)	62 (21.2)	105 (13.7)
Duration of diabetes, years	8.8 ± 6.3	8.2 ± 5.2	8.9 ± 6.7	9.6 ± 5.8	9.0 ± 6.1
HbA1c					
Mmol/Mol	59.3 ± 7.8	63.2 ± 8.5	63.7 ± 8.2	72.6 ± 10.6	65.4 ± 10.8
%	7.6 ± 0.7	7.9 ± 0.8	8.0 ± 0.8	8.8 ± 1.0	8.1 ± 1.0
Weight, kg	84.9 ± 19.0	83.2 ± 19.2	86.0 ± 19.0	88.7 ± 17.6	86.3 ± 18.6
Baseline FG					
Mmol/L	7.0 ± 0.9	7.4 ± 0.7	9.3 ± 0.7	10.8 ± 2.0	8.8 ± 2.2
Mg/dL	126.3 ± 15.8	134.1 ± 11.8	167.3 ± 12.3	195.1 ± 35.4	158.4 ± 39.9
Baseline PPG					
Mmol/L	8.4 ± 1.1	11.5 ± 1.2	9.1 ± 0.8	12.9 ± 2.2	10.6 ± 2.6
Mg/dL	150.5 ± 20.5	206.9 ± 20.7	163.5 ± 14.0	233.0 ± 39.8	190.2 ± 47.5

Data presented as mean ± SD unless otherwise specified.

Abbreviations: FG, fasting glucose; HbA1c, glycosylated haemoglobin; PPG, postprandial glucose.

<sup>a</sup>Canada and Australia.

covariance (ANCOVA) with treatment, subgroup and treatment by subgroup interaction as fixed effects. Changes from baseline in weight were analysed using ANCOVA with treatment, subgroup and treatment by subgroup interaction as fixed effects and baseline weight as covariate. Last post-baseline observation was carried forward to impute missing post-baseline values. Baseline data are presented as mean (SD) or n (%), and changes from baseline data are presented as least squares means (LSM) and standard errors (SE) or 95% confidence interval (CI). Counts and percentages of participants reporting hypoglycaemia, as well as insulin units at endpoint are described. Given the nature of this non-prespecified post hoc analysis, only associations can be concluded from the results obtained.

### 3 | RESULTS

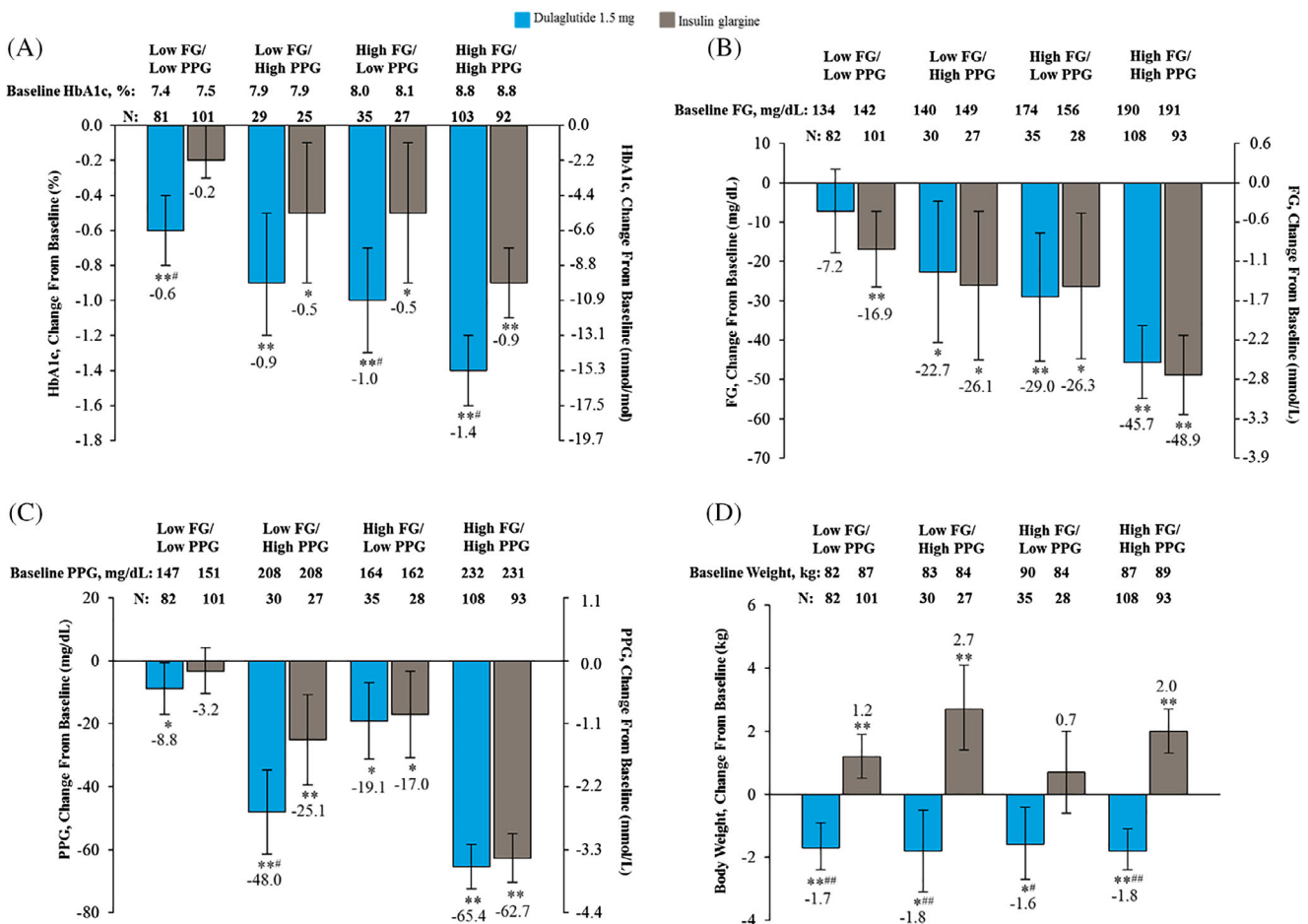
#### 3.1 | Baseline characteristics

Overall, 766 participants were included in this post hoc analysis (low FG/low PPG,  $n = 292$ ; low FG/high PPG,  $n = 90$ ; high FG/low PPG,

$n = 92$ ; high FG/high PPG,  $n = 292$ ). The subgroup with high FG/high PPG was associated with the longest mean duration of diabetes, highest baseline HbA1c, and highest body weight, versus the other subgroups (Table 1).

#### 3.2 | Change in HbA1c

At 52 weeks, significant reductions from baseline in HbA1c were observed in all subgroups with dulaglutide 1.5 mg and with glargine (all  $P < .05$ ), except in the low FG/low PPG subgroup with glargine (Figure 1A). Overall, the greatest reductions were observed in the high FG/high PPG subgroup at baseline (dulaglutide 1.5 mg:  $-1.4\%$ ; glargine:  $-0.9\%$ ), and the smallest reductions were observed in the low FG/low PPG subgroup at baseline (dulaglutide 1.5 mg:  $-0.6\%$ ; glargine:  $-0.2\%$ ) [Figure 1A]. At 52 weeks, dulaglutide 1.5 mg treatment was associated with a greater reduction in HbA1c when compared with glargine across all subgroups (Figure 1A). Observed treatment effects of the two drugs significantly differed among participants with low FG/low PPG, high FG/low PPG, and high FG/high



**FIGURE 1** Change from baseline in glycaemic measures and body weight at 52 weeks by subgroups in people treated with dulaglutide 1.5 mg or insulin glargine. Data presented as least squares mean (95% CI); intention-to-treat population, without post-rescue visits. \* $P < .05$  and \*\* $P < .001$  change from baseline. # $P < .05$  and ## $P < .001$  vs. insulin glargine. (A), Change from baseline in glycated haemoglobin (HbA1c) at 52 weeks. (B), Change from baseline in fasting glucose (FG) at 52 weeks. Glucose values for FG are from self-monitored plasma glucose. (C), Change from baseline in postprandial glucose (PPG) at 52 weeks. Glucose values for PPG are from the central laboratory. (D), Change from baseline in body weight at 52 weeks

PPG at baseline in favour of dulaglutide 1.5 mg (LSM treatment difference:  $-0.4\%$  [95% CI  $-0.7, -0.2$ ],  $P = .003$ ;  $-0.5\%$  [95% CI  $-1.0, -0.0$ ],  $P = .049$ ; and  $-0.4\%$  [95% CI  $-0.7, -0.2$ ],  $P = .002$ , respectively).

### 3.3 | Change in FG and PPG

At 52 weeks, significant reductions from baseline in FG were observed in all subgroups with dulaglutide 1.5 mg and with glargine (all  $P < .05$ ), except in the low FG/low PPG subgroup with dulaglutide 1.5 mg (Figure 1B and Table S1). Overall, the greatest reductions were observed in the high FG/high PPG subgroup (dulaglutide 1.5 mg:  $-45.7$  mg/dL [ $-2.5$  mmol/L]; glargine:  $-48.9$  mg/dL [ $-2.7$  mmol/L]), and the smallest reductions were observed in the low FG/low PPG subgroup (dulaglutide 1.5 mg:  $-7.2$  mg/dL [ $-0.4$  mmol/L]; insulin glargine:  $-16.9$  mg/dL [ $-0.9$  mmol/L] [Figure 1B and Table S1]). Observed differences between the two treatments were not significant within any subgroup.

At 52 weeks, significant reductions from baseline in PPG were observed in all subgroups with dulaglutide 1.5 mg and with glargine (all  $P < .05$ ), except in the low FG/low PPG subgroup with glargine (Figure 1C and Table S1). Overall, the greatest reductions were observed in the high FG/high PPG subgroup (dulaglutide 1.5 mg:  $-65.4$  mg/dL [ $-3.6$  mmol/L]; glargine:  $-62.7$  mg/dL [ $-3.5$  mmol/L]), and the smallest reductions were observed in the low FG/low PPG subgroup (dulaglutide 1.5 mg:  $-8.8$  mg/dL [ $-0.5$  mmol/L]; glargine:  $-3.2$  mg/dL [ $-0.2$  mmol/L] [Figure 1C and Table S1]). Treatment with dulaglutide 1.5 mg was associated with greater reductions in PPG than glargine only among participants with low FG/high PPG (LSM treatment difference:  $-23.0$  mg/dL [ $-1.3$  mmol/L] [95% CI  $-42.6$  ( $-2.4$ ),  $-3.4$  ( $-0.2$ )];  $P = .021$ ).

### 3.4 | Change in body weight

At 52 weeks, treatment with dulaglutide 1.5 mg was associated with significant reductions in body weight from baseline across all subgroups, while treatment with glargine was associated with significant increases in body weight from baseline in participants with low FG/low PPG, low FG/high PPG and high FG/high PPG (Figure 1D). The observed treatment effects of the two drugs significantly differed and favoured dulaglutide in all subgroups (LSM treatment difference: low FG/low PPG  $-2.8$  kg [95% CI  $-3.9, -1.8$ ],  $P < .001$ ; low FG/high PPG  $-4.5$  kg [95% CI  $-6.4, -2.6$ ],  $P < .001$ ; high FG/low PPG  $-2.3$  kg [95% CI  $-4.0, -0.5$ ],  $P = .012$ ; and high FG/high PPG  $-3.8$  kg [95% CI  $-4.7, -2.8$ ],  $P < .001$ ).

Similar baseline characteristics were observed in participants treated with dulaglutide 0.75 mg; however, dulaglutide 0.75 mg was associated with greater reduction in HbA1c from baseline compared to glargine only in the low FG/low PPG subgroup (Figure S2A). In the high FG/high PPG subgroup, observed FG reductions were significantly greater with glargine than with dulaglutide 0.75 mg ( $P < .05$ ; Figure S2B and Table S2), whereas observed reductions in PPG were similar among the two treatments across all subgroups (Figure S2C

and Table S2). Treatment with dulaglutide 0.75 mg was associated with significantly reduced body weight across all subgroups (Figure S2D).

### 3.5 | Safety

The complete safety profile for AWARD-2 was previously reported.<sup>8</sup> At 52 weeks, observed documented symptomatic hypoglycaemia was consistently lower with dulaglutide 1.5 mg versus glargine (Table S3). Observed glargine dose (median [min, max]) at 52 weeks was highest in the high FG/high PPG group (0.32 [0.00, 0.94] units/kg) and lowest in the low FG/high PPG group (0.18 [0.07, 1.39] units/kg [Table S3]). Similar safety results were observed in participants treated with dulaglutide 0.75 mg (Table S4).

## 4 | DISCUSSION

In the present post hoc analysis, we investigated the efficacy of once-weekly dulaglutide compared to glargine in people with T2D and differing baseline glycaemic patterns. Overall, a greater improvement in glycaemic control, expressed as reductions in HbA1c levels, was observed with dulaglutide compared to glargine, despite varying baseline FG and PPG levels. Furthermore, observed differences among these two treatments were substantially conserved despite their distinct mechanisms of action and effects on FG and PPG.

Different glycaemic patterns may suggest different pathophysiological defects (hepatic glucose overproduction, insulin resistance, reduced insulin secretion) that occur over the duration of T2D and impact FG and PPG. FG elevations are thought to occur later in the course of the disease, whereas postprandial elevations usually appear earlier. However, in the AWARD-2 study cohort, duration of diabetes was similar across the different glycaemic subgroups, suggesting the existence of distinct glycaemic patterns rather than differences in glycaemic patterns attributable to disease progression. We believe these results are of interest, given the increasing importance of addressing both fasting and postprandial hyperglycaemia when treating T2D, and the availability of anti-hyperglycaemic medications addressing FG and PPG, respectively, to a different extent.

The greatest reduction overall in HbA1c was observed in the high FG/high PPG subgroup for both treatments. This subgroup was also associated with higher baseline HbA1c levels, and thus greater HbA1c reductions were to be expected. As suggested by previous reports,<sup>10,11</sup> our initial hypothesis was that glargine would be associated with better efficacy over dulaglutide in the subgroup with prevalent high FG at baseline, whereas dulaglutide would be associated with predominant efficacy over glargine in the subgroup with prevalent high PPG at baseline. However, dulaglutide 1.5 mg was associated with higher HbA1c reductions than glargine also in the high FG/low PPG subgroup, even though observed FG levels at 52 weeks tended to be lower with glargine than with dulaglutide 1.5 mg, reflecting the greater effect of FG-driven basal insulin titration on fasting hyperglycaemia. The observed results could potentially be

explained by dulaglutide reducing both FG and PPG, as well as glucose levels throughout the day, as demonstrated across the phase 3 clinical trials with this GLP-1RA.<sup>8,12-16</sup> The superiority of dulaglutide 1.5 mg in reducing HbA1c, however, was also observed in the larger group with both high FG and high PPG at baseline, and is consistent with the overall study results. Nevertheless, the observed efficacy of dulaglutide 1.5 mg in reducing PPG can be appreciated in the low FG/high PPG subgroup, in which dulaglutide 1.5 mg was associated with greater PPG reductions than glargine.

Across subgroups, dulaglutide was associated with statistically greater body weight reductions compared to the weight gain observed with glargine, consistent with results reported in the primary AWARD-2 manuscript.<sup>8</sup> Likewise, observed total hypoglycaemia was consistently lower with dulaglutide compared to glargine, particularly in the high PPG subgroups. As expected, greater increases in glargine dose were observed at 52 weeks in subgroups with high FG, given that glargine was titrated according to FG, and thus a higher median dose was required to control a higher degree of fasting hyperglycaemia.

A limitation of this study was the post hoc and non-prespecified nature of the analysis. The duration of this study was limited to 78 weeks (52 weeks was the primary endpoint), which may not represent the effects of long-term use of dulaglutide. Additionally, this post hoc analysis included small sample sizes, especially for the low FG/high PPG and high FG/low PPG subgroups. Due to the limited sample size, the median was chosen as the cut-off, which may have influenced the results as the glycaemic pattern was less strictly defined; thus, the data presented should be considered as hypothesis-generating only. Lastly, as reported in the primary AWARD-2 study, the mean total daily glargine dose at 52 weeks was 29 units.<sup>8</sup> A central committee monitoring insulin adjustments was not employed, and thus, strict enforcement of the insulin titration algorithm was not accomplished. Although the total glargine dose was consistent with the average dose in other similar clinical trials,<sup>17-19</sup> it is possible that a stricter titration monitoring could have resulted in lower mean FG, leading to greater decrease in HbA1c with glargine.

In conclusion, this non-prespecified post hoc analysis of the AWARD-2 study shows that treatment with once-weekly dulaglutide is associated with improved glycaemic control regardless of baseline FG and PPG levels. These data suggest that this long-acting GLP-1RA can be a valid treatment option in people with T2D at different levels of disease severity and with different glycaemic patterns.

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## CONFLICT OF INTEREST

F.G. serves or has served on the advisory boards for AstraZeneca, Eli Lilly and Company, Roche Diabetes Care, and NovoNordisk, serves or

has served as a consultant for AstraZeneca, Boehringer-Ingelheim, Lifescan, Merck Sharp & Dohme and Sanofi, and has received research support from AstraZeneca, Eli Lilly and Company, Lifescan and Takeda. M.Y., Z.M., A.H. and L.E.G.P. are employees and shareholders of Eli Lilly and Company.

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## AUTHOR CONTRIBUTIONS

All authors contributed to the study design. M.Y. was responsible for the statistical considerations in the analysis and trial design. L.E.G.P. is the guarantor of this work and, as such, takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors participated in critical reviewing and interpreting the data for the manuscript. All authors had full access to all data related to this report and had final responsibility for the decision to submit for publication.

## ORCID

Francesco Giorgino  <https://orcid.org/0000-0001-7372-2678>

Axel Haupt  <https://orcid.org/0000-0003-4502-0470>

Zvonko Milicevic  <https://orcid.org/0000-0002-6746-901X>

Luis-Emilio García-Pérez  <https://orcid.org/0000-0003-3840-787X>

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## SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

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