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Considerations on the Weight Loss Associated Glucagon Like Peptide-1 Receptor Agonists for Older Adults

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Obesity rates in seniors have increased around the world[1] with rates tripling over the past four decades.[2] While previously considered a phenomenon of developed countries, the increased prevalence of obesity is now established in developing countries as well.[3] Factors stimulating this epidemic include modifications in the global food supply chain, rise in consumption and availability of energy-dense, low-nutrient foods, sedentary occupations, expanding urbanization, changes in transportation means, as well as environmental components.[3] The increasing prevalence of obesity in older adults in the US over time has been well documented by federal agencies. Over the time periods 1999–2002, 2003–2006, and 2007–2010, a linear increase in the prevalence of obesity among older men in all age groups was observed. The obesity prevalence among men aged 65−74 increased from about 31.6% in 1999–2002 to 41.5% in 2007–2010. In men over 74, obesity prevalence increased from 17.7% in 1999−2002 to 26.5% in 2007–2010. Interestingly, in women, the change over the same time period was not statistically significant for the older age groups (40.3% obesity in 65 to 74 year old women and 28.7% in women over 74 years old in 2007-2010 analysis period).[4]

The incidence of type II diabetes, all cancers except esophageal and prostate cancer, all cardiovascular diseases, asthma, gallbladder disease, osteoarthritis and chronic back pain demonstrated statistically significant associations with obesity in a systematic review and meta-analysis of studies completed in Western Countries. In this study, the strongest association was observed with obesity and the incidence of type II diabetes in females. The study authors concluded that maintenance of a healthy weight could be important in the prevention of future large disease burden.[5] Patients with obesity are also more likely to be hospitalized. Four of the five most frequent diagnoses at hospital admission in older adults are associated with obesity (congestive heart failure, coronary atherosclerosis, cardiac dysrhythmias and acute myocardial infarctions, all which have associations with obesity).[6] The economic impact of obesity has also begun to be characterized with an estimate using the US Medical Expenditure Panel Survey[7] finding that obesity-attributable medical expenditures were estimated at $75 billion with roughly one-half of these expenditures are financed by the public Medicare and Medicaid funds. A microsimulation study that estimated lifetime costs, longevity, disease, and disability for seventy-year-olds based on body mass found that 70 year old people with obesity will live roughly as long as those of normal weight. However, they will spend more than $39,000 more on health care and will experience fewer disability-free life years with higher rates of diabetes, hypertension, and heart disease. The prediction model found that Medicare will spend approximately 34 percent more on an obese person than on someone of normal weight. The study authors also proposed that obesity might result in higher costs for Medicare compared to other diseases, since higher costs are not offset by reduced longevity as seen with other chronic diseases in developed countries.[8]

Evidence continues to build on the clinical benefits of the Glucagon Like Peptide-1 (GLP-1) Receptor Agonists (RAs).[9] The most recent published findings in a randomized clinical trial of patients with median age of 69 has provided fresh evidence on the effectiveness of the GLP-1 RAs in older adults. In the Semaglutide Treatment Effect in People with obesity and Heart failure with preserved ejection fraction (STEP-HFpEF) trial demonstrated larger reductions in symptoms and physical limitations, greater improvements in exercise function, and greater weight loss for patients randomized to semaglutide compared to patients taking placebo. The average percent drop in body weight was 13.3% with semaglutide versus 2.6% with placebo with an estimated

statistically significant increase in weight loss of 10.7 percentage points with semaglutide with P-value of <0.01. The mean improvement in the 6-minute walk distance was 21.5 meters with semaglutide and 1.2 meters with placebo with an estimated statistically significant increase of 20.3 meters with semaglutide with P-value P<0.01). The mean percent drop in the C-reactive protein (CRP) level was also statistically superior for semaglutide with a 43.5% reduction compared to 7.3% for placebo (P-value <0.01). Fewer serious adverse events (SAEs) were reported in the semaglutide trial arm with 35 participants (13.3%) reporting SAEs in the semaglutide group versus 71 (26.7%) SAEs in the placebo arm.[10]

Many considerations persist from the lens of clinical outcomes, economic consequences, and logistical complexities that are magnified in older adults. The bulk of clinical trials completed had limited representation of older adults although as STEP-HFpEF demonstrated that is beginning to change. Understanding the drug interaction possibilities in older adults who are more likely to have multimorbidity and polypharmacy is a key consideration. Adverse events seen included dehydration, nausea, vomiting,[11] and reduction in muscle mass observed after weight loss treatments in general has been well documented in the scientific literature.[12] Each of these pose particular concerns in older adults who are already at elevated risk for falls and fractures.[13] Potential long term possible risks include medullary thyroid carcinoma or multiple endocrine neoplasia syndrome.[14] Reductions in weight may also translate to required gradual dose reduction or deprescribing of medications to treat diabetes or hypertension as well as the GLP-1 RA itself. In terms of possible financing challenges, an analysis that applied the US Centers for Disease Control and Prevention's estimated obesity prevalence for adults 60 years of age and above (41.5%) that varied medication uptake ranging from 1% and 100% in order to calculate possible yearly Medicare Part D medication spend. Under a simulated scenario where all beneficiaries with obesity use semaglutide for weight loss, the spend would eclipse the entire Part D budget. Moreover, this would exceed the total excess health care spending associated with obesity for people of all ages. This was a conservative economic measure of impact given that these estimates excluded the costs associated with possible antiobesity-medication use by people who are overweight.[15] With an estimated U.S. price for subcutaneous semaglutide after incorporating rebates and discounts of $13,618 per year per person for weight loss management,[16] and an awareness that the medication will needed to be taken long-term and, potentially, life-long, the challenge is clear in terms of population-level economics. Within a year of the approval of semaglutide for obesity, shortages were reported due to spiking demand and insufficient manufacturing quantity. The ripple effect of these shortages led to shortages of semaglutide for patients with diabetes.[17]

Multiple authors have recommended the need for long-term monitoring in observational datasets to characterize use in real-world patient populations.[15,17] We conducted an analysis of GLP-1 RA users that applied data from the University of California Health Data Warehouse that included health data from the six academic health centers of the University of California system in the period of January 1, 2014 to June 30, 2023 that included 110 562 distinct users (Table 1). This analysis found that sizeable proportions of the total users were older adults (Figure 1). This included the GLP-1 RA products that received formal FDA approval for weight loss as several are approved for patients with diabetes and not approved weight loss heretofore. Among the users of the three semaglutide products Ozempic, Wegovy, and Rybelsus, more than 70% were 50 years old and above and more than 30% were 65 years old and above (Table 2). It is evident that more studies are needed in older adults to determine best practices and to shape policy that will ensure maximum benefit to society. Given the high cost, supply challenges, and increasing relevance in developing and developed countries, it is also important to ensure equitable access is an explicit goal.

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Table 1. Glucagon-like Peptide 1 Receptor Agonists (GLP-1 RA) Summary Data in the University of California Health Data Warehouse (1/1/14 to 6/30/23)

Glucagon-like Peptide 1 Receptor Agonists Distinct Users Total Count	110 562
Average Age	57.7
Median Age	59
Under 50	29 263
Between 50 and Under 65	43 445
65 and Over	37 854

Table 2. Summary Data by Glucagon-like Peptide 1 Receptor Agonists (GLP-1 RA) by Brand Name

GLP-1 RA by Brand Name*	Byetta (exenatide SQ)	Mounjaro (tirzepatide SQ)	Ozempic (semaglutide SQ)	Rybelsus (semaglutide oral)	Saxenda (liraglutide SQ)	Trulicity (dulaglutide)	Victoza (liraglutide SQ)	Wegovy (semaglutide SQ)
Count†	1 484	3 221	42 893	10 927	6 180	39 603	17 788	10 340

Average Age	60.4	54	57.5	61	46.7	61.1	59.1	47.2
Median Age	61	54	59	62	47	62	61	48
Under 50	258	1 177	11 448	2 069	3 429	6 895	3 857	5 684
Between 50 and Under 65	640	1 258	17 035	4 092	2 376	15 744	7 165	3 964
65 and Over	586	786	14 410	4 766	375	16 964	6 766	682

*Brand Name GLP-1 RA Adlyxin was not included in table due to cell counts under 30.

† Grand total count across rows will not equal Table 1 total count as users may user more than one agent. Adlxyin was also removed.