



83rd Scientific Sessions

SAN DIEGO, CA / HYBRID | JUNE 23-26, 2023

•• CONFERENCE COVERAGE JOURNAL ••

Debate Weighs the Efficacy of Initial Combination Therapy for Type 2 Diabetes

The effectiveness of initial combination therapy for type 2 diabetes is the topic of discussion.

During “Are Two Better than One?” experts debated the merits of initial combination therapy versus sequential therapy. At the 83rd Scientific Sessions, Initial Combination Therapy for Type 2 Diabetes Mellitus was presented.

Professor of Medicine at the University of Texas Health Science Center at San Antonio, Ralph A. DeFronzo, MD, advocated for the initial use of combination therapy due to its ability to effectively correct multiple pathophysiological defects. Additionally, he claimed that monotherapy caused delays in initiating appropriate treatments.

Multiple primary pathophysiologic defects are caused by type 2 diabetes:

- Decreased insulin secretion
- Decreased incretin effect
- Increased lipolysis
- Increased glucose reabsorption
- Decreased glucose uptake
- Neurotransmitter dysfunction

Dr. DeFronzo affirmed, "You'll need multiple medications to treat these eight conditions, and you'll have to take them in combination."

In addition to lowering A1C levels, he emphasized that the prescribed medications should target known pathogenic abnormalities. To prevent progressive beta-cell failure, it is also essential that patients begin treatment early in the course of type 2 diabetes.

Dr. DeFronzo recommended a glucagon-like peptide-1 (GLP-1) receptor agonist, sodium-glucose cotransporter-2 (SGLT2) inhibitor, and pioglitazone for all patients as an initial combination therapy regimen. He also highlighted metformin for managing A1C, but cautioned that unlike the other three medications, it does not help patients with type 2 diabetes with cardiovascular, renal, or metabolic problems.

"When we consider therapy, there is simply no way that one drug can treat all of these issues," Dr. DeFronzo said.

Dr. DeFronzo cited the randomized trial Efficacy and Durability of Initial Combination Therapy for Type 2 Diabetes (EDICT) in support of his argument. EDICT compared the outcomes of initial combination therapy with metformin, pioglitazone, and exenatide to sequential add-on therapy with metformin, glipizide, and glargine. After three years of treatment, the number of patients in each cohort with A1C levels below 6.5% was determined.

"With the triple therapy, 70% of patients had an A1C of less than 6.5%, whereas 71% of patients failed with the conventional therapy of metformin, sulfonylurea, and insulin," DeFronzo said

Dr. DeFrancisco referred to monotherapy as the "treat to fail" strategy. Even after an initial decline, he argued that prescribing one drug at a time and evaluating its effects on a patient would inevitably result in an increase in A1C over time. This is also a time-consuming procedure that can prevent clinicians from managing the progression of retinopathy or albuminuria early in type 2 diabetes's history.

Dr. DeFrancisco stated, "the quicker you initiate control and the better the control, the less likely long-term complications will occur."

David M. Nathan, MD, Director of the Clinical Research Center and the Diabetes Center at Massachusetts General Hospital and Professor of Medicine at Harvard Medical School, argued that sequential therapy is a more verifiable and efficient initial approach to managing type 2 diabetes than combination therapy due to its lower cost and the ability to individualize therapies for patients based on their response to a drug while measuring the side effects of individual drugs. In addition, he questioned the validity of trial data supporting the initial implementation of combination therapy.

Similarly, to Dr. DeFronzo, he examined the EDICT study, which he described as one of the few studies that analyzed the effects of various therapies over an extended period of time. However, he argued that the data demonstrated only marginal overall benefits for patients receiving combination therapy, in addition to a significant disadvantage: cost. According to him, the monthly cost of combination therapy in the United States is approximately \$1,300, whereas sequential treatment costs \$85 per month.

"The additional annual cost of initiating this combination therapy in, say, the 1.5 million new cases of type 2 diabetes each year in the United States would be \$22 billion," Dr. Nathan stated.

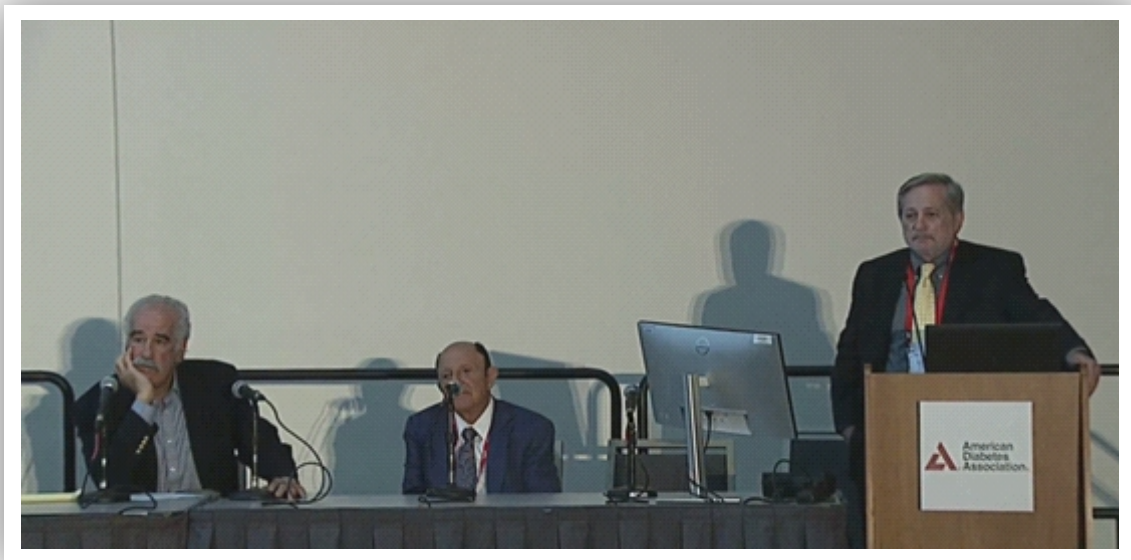
Dr. Nathan also argued that combination therapies fail to provide providers with valuable insights that allow for an individualized treatment approach. When multiple drugs are administered to a patient simultaneously, it is impossible for the physician to evaluate the benefits and side effects of each individual drug.

Dr. Nathan also evaluated PubMed data from studies that compared the efficacy of combination therapies versus monotherapy for the initial treatment of type 2 diabetes and found 19 unique randomized controlled trials.

Dr. Nathan stated, "Generally, initial combination therapy has only been evaluated for brief, clinically insufficient periods; consequently, I believe sequential therapy is still required."

Over the course of several years, the comparative benefits of combination therapy decreased over time, as evidenced by a decline in the initial correlation between A1C levels and combination therapy.

"We must be wary of these early studies because they are not comparable to clinically significant duration studies," Dr. Nathan cautioned.



Dr. Nathan also noted that sixteen of the nineteen studies compared combination therapy to monotherapy, rather than sequential therapy. Sequential therapy permits a provider to observe the effects of a substance on a patient before, if necessary, switching to a different treatment. Studies of monotherapy examine a singular form of treatment without follow-up. According to Dr. Nathan, these investigations do not accurately replicate a clinical approach.

Before adopting initial early combination therapy as the standard of care, "well-powered, acceptable-duration studies must be conducted," he explained.