

November 11, 2018

AHA 2018 - AstraZeneca takes heart from partial Farxiga victory



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The Declare-Timi trial's success was driven by a decrease in cardiovascular hospitalisations rather than deaths, but Astra put this down to the lower-risk population studied.

Astrazeneca's Farxiga has become the third SGLT2 inhibitor to show a benefit on cardiovascular outcomes. But working out how the diabetes drug stacks up against its rivals - Lilly and Boehringer's Jardiance, and Johnson & Johnson's Invokana - is difficult.

On the face of it Farxiga looks to have fallen short of the competition with full results from the Declare-Timi trial, presented at the American Heart Association conference yesterday. But the picture is complicated by the fact that the companies chose to study slightly different populations of diabetes patients in their big outcomes studies.

Indeed, Astra believes that its decision to enrol mainly primary prevention patients might end up standing it in good stead. Around 60% of the 17,000 subjects in Declare-Timi were merely at risk of cardiovascular events, while the rest had had established cardiovascular disease.

By contrast, all patients in the Empa-Reg Outcome trial of Jardiance had both diabetes and cardiovascular disease, while the Canvas study of Invokana was split around 70:30 in favour of the secondary prevention population.

SGLT2 inhibitor cardiovascular outcomes trials

Product	Company	Trial	Population	Result
Farxiga	Astrazeneca	Declare-Timi, NCT01730534	60% primary prevention, 40% secondary prevention	Non-inferior on MACE-3; 17% reduction in risk of CV death or hospitalisation
Jardiance	Lilly/Boehringer Ingelheim	Empa-Reg Outcome, NCT01131676	All secondary prevention	14% reduction in MACE
Invokana	Johnson & Johnson	Canvas, NCT01032629	30% primary prevention, 70% secondary prevention	14% reduction in MACE

Source: Company releases, Clinicaltrials.gov.

This might explain why [Declare-Timi was unable to show a benefit on one of its co-primary endpoints](#), a composite of cardiovascular death, myocardial infarction or stroke - which are more likely to happen in sicker patients. Both Jardiance and Invokana demonstrated a 14% reduction in the risk of such events.

However, Astra was lucky - or wise - in that it added a co-primary endpoint to Declare-Timi before unblinding the study. This outcome, a composite of cardiovascular death or hospitalisation, hit significance, something that Astra had already disclosed ([Astra not too timid to declare Farxiga victory, September 24, 2018](#)).

Class effect?

At AHA yesterday the company gave more details. Treatment with Farxiga reduced the risk of cardiovascular death or hospitalisation by 17%; however, this was entirely driven by a benefit on the hospitalisation part of this endpoint, and there was no impact on cardiovascular death.

Elisabeth Björk, head of Astra's cardiovascular, renal and metabolic division, was unconcerned, telling *Vantage*: "One possible reason is that our patient population was healthier than the population in the other [studies]."

As well as including primary prevention patients, the secondary prevention cohort was less sick than in other SGLT2 outcomes trials, she added. Declare-Timi excluded patients with a creatinine clearance, a measure of kidney function, of less than 60ml per minute.

"To us the most important finding is that you have this massive reduction of heart failure across this broad patient population; this is an everyday population that physicians are seeing," Ms Björk concluded.

Also importantly, Declare-Timi did not find an increase in the rate of amputations, a problem that has dogged Invokana.

So Farxiga's main competitor looks likely to be Jardiance. When asked how doctors might pick between the two, Danilo Verge, Astra's vice-president of global medical affairs, replied: "If a doctor is forced to choose, based on available data, we can say we're the only company that has data spanning the totality of diabetes populations."

He added: "We can now say unequivocally that Farxiga should be considered in any patient with type 2 diabetes walking through the door of a GP's office."

But Astra is not stopping at patients with diabetes. The company also has ongoing trials of Farxiga in heart failure and kidney disease patients, regardless of whether they have diabetes or not, with the first data due in 2020.

Lilly and Boehringer also have active studies of Jardiance in heart failure irrespective of diabetes.

Jardiance and Invokana both have cardiovascular risk reduction on their labels. The results from Declare-Timi provide more evidence of a class effect.

Moving outside diabetes: selected SGLT2 trials

Study	Setting	Trial ID	Data due
Farxiga			
Dapa-HF	Heart failure with reduced ejection fraction	NCT03036124	2020
Deliver	Heart failure with preserved ejection fraction	NCT03619213	"2020 onwards"
Dapa-CKD	Chronic kidney disease	NCT03036150	2020
Jardiance			
Emperial-Reduced	Heart failure with reduced ejection fraction	NCT03448419	2019
Emperial-Preserved	Heart failure with preserved ejection fraction	NCT03448406	2019
Emperor-Reduced	Heart failure with reduced ejection fraction	NCT03057977	2020
Emperor-Preserved	Heart failure with preserved ejection fraction	NCT03057951	2020
<i>Source: Clinicaltrials.gov</i>			