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ATTR-CM Survey - Silencers ± Combo Are Likely to Gain at the Expense of Stabilizer Monotherapy

Key Message: We conducted a survey of 30 U.S. cardiologists treating an average of 50 ATTR-CM patients. Survey respondents indicate (1) stabilizers remain the largest class both among all treated patients and newly diagnosed cases, currently; (2) over the next 2 years, ~2/3 physicians expect to increase their use of silencers in first line, either as monotherapy or in combination with a stabilizer; (3) none of the physicians expect silencer use in first line to decrease; (4) Silencer or silencer + stabilizer combination are the second-line treatment of choice for ~80% of patients that experience disease progression on a stabilizer; (5) potential approval of WAINUA is likely to increase the use of silencers.

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Companies impacted: ALNY, PFE, BBIO, AZN, IONS

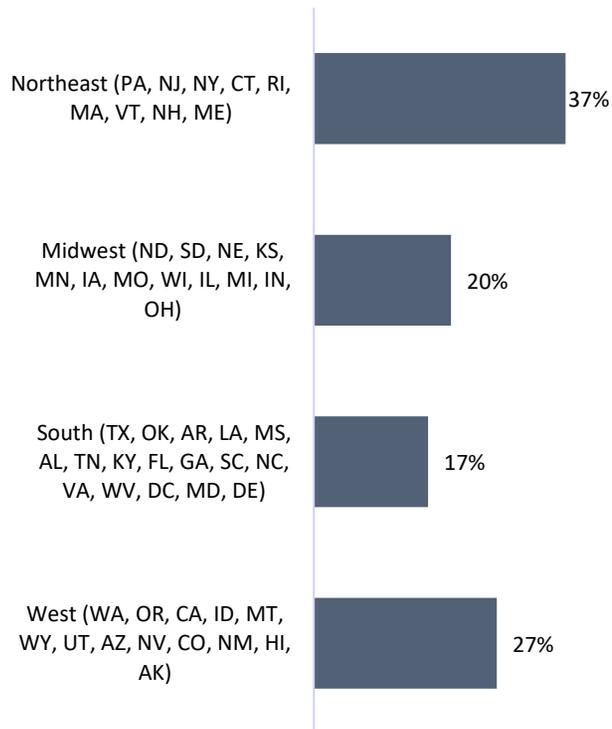
Our survey has feedback from 30 U.S. cardiologists who collectively treat 2,251 patients with ATTR-CM. Physicians are well-represented geographically and are primarily practicing in urban (57%) and suburban (43%) areas. On average, they care for 50 patients each (range 20-150), excluding mixed phenotype PN / CM patients.

Key takeaways include

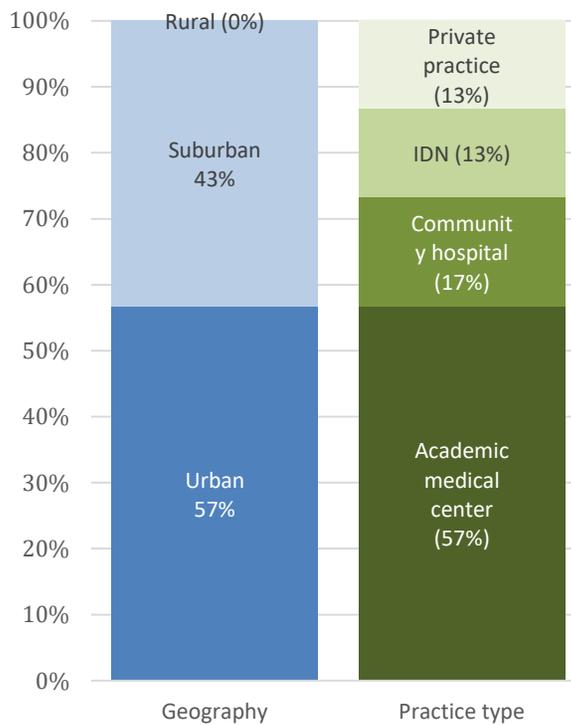
1. Among surveyed physicians, Vyndaqel / Vyndamax remains the most commonly used agent; Attruby is gaining market share among newly diagnosed patients.
2. Combinations of stabilizer + silencer are currently largely relegated to patients with disease progression on monotherapy.
3. 30% of surveyed physicians have not yet prescribed Amvuttra. Similarly, 30% of physicians have not yet prescribed Attruby. For both drugs, patients being well controlled on their current agents is the main reason these physicians have not yet used Amvuttra / Attruby.
4. ~63% of surveyed physicians expect to increase their use of silencers for newly diagnosed patients either as a monotherapy or as stabilizer + silencer combination over the next 2 years. None of the surveyed physicians expect the use of silencers in first line to decrease over the same time frame.
5. The projected shift to more silencer / combination use comes mostly at the expense of Vyndaqel / Vyndamax monotherapy. Attruby's share remains largely unchanged on average, with ~30% of surveyed physicians expecting to increase Attruby use in 1L, mostly by replacing Vyndaqel / Vyndamax, while ~17% expect 1L use of Attruby to decrease, shifting towards silencer monotherapy or combo of silencer + Vyndaqel / Vyndamax.
6. Efficacy remains the most impactful criterion for physicians when choosing a first-line treatment.
7. Newly diagnosed hATTR-CM patients are more likely to be treated with a silencer compared to wtATTR-CM.
8. Amvuttra administration is spread evenly between prescriber practice and infusion centers; buy-and-bill is the biggest challenge for Amvuttra prescribers.
9. Upon disease progression, physicians are more likely to switch patients from a stabilizer to a silencer (40% of patients on average) or onto combination therapy (40%) vs. switching them to a different stabilizer (20%).
10. In the eyes of the clinicians, efficacy remains the principal unmet need of ATTR-CM patients, indicating room for next-generation agents (e.g., Alnylam's nucusiran).
11. Physicians anticipate approval of WAINUA in ATTR-CM to grow the market of silencers in favor of stabilizers but would only switch a minority of patients.

The survey was conducted among board-certified U.S. cardiologists from a broad range of practice settings

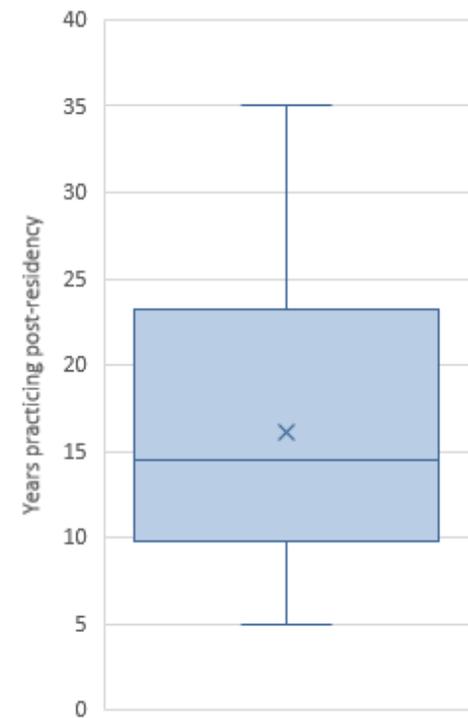
In what region is your practice/your organization located? (n=30)



Which of the following best describes your current organization? (n=30)



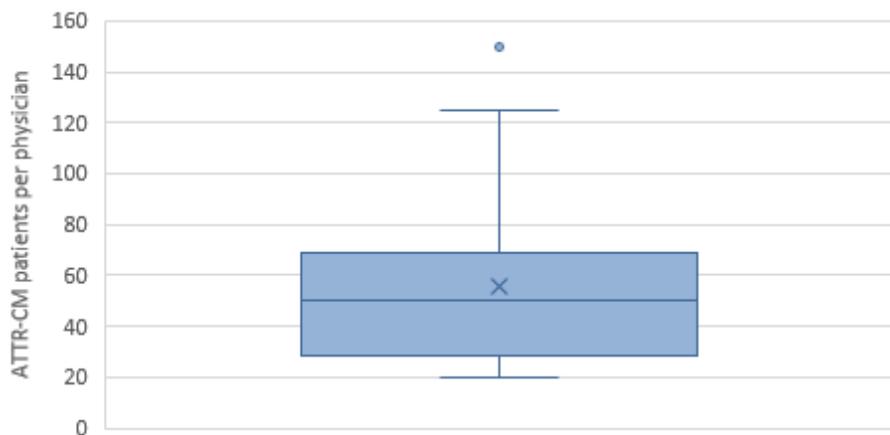
For how many years have you been practicing (post-residency)? (n=30)



Source: Guggenheim Securities, LLC survey, n=30

Surveyed physicians collectively care for 2,251 ATTR-CM patients, ~25% of which are CM / PN mixed phenotype

Approximately how many patients with ATTR-CM are currently under your care, excluding CM / PN mixed phenotype? (n=30)



■ ATTR-CM total patient n = 1680 (Excludes ATTR-CM / PN mixed phenotype)

Approximately how many patients with ATTR-CM / PN mixed phenotype are currently under your care? (n=30)



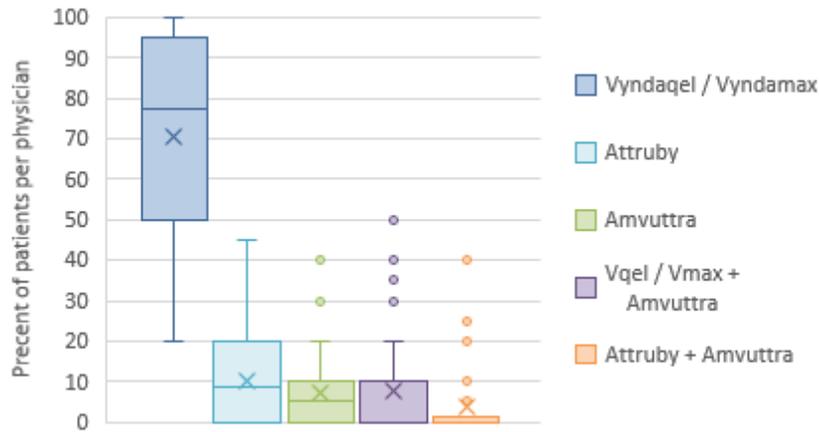
■ ATTR-CM / PN mixed phenotype total patient n = 571

	Total number of patients	Average number of patients per physician	Median number of patients per physician	Range of patients per physician
ATTR-CM (excl. mixed phenotype)	1680	56	50	20-150
ATTR-CM / PN mixed phenotype	571	19	15	0-75
Total	2251	75	60	28-175

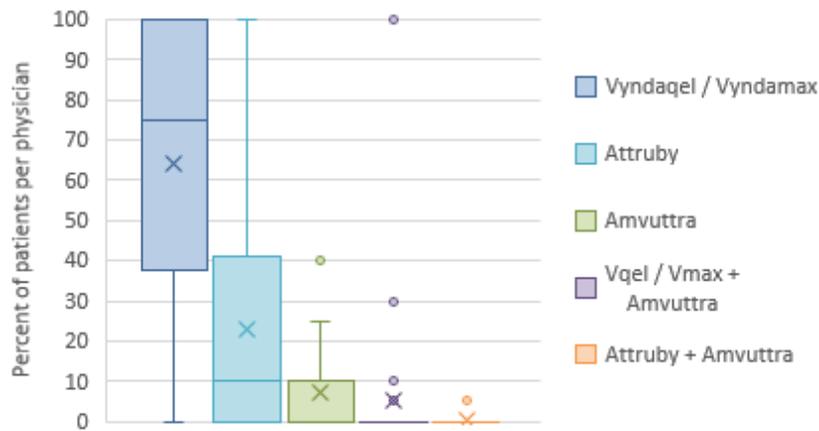
Source: Guggenheim Securities, LLC survey, n=30

Among surveyed physicians, Vyndaqel / Vyndamax remains the most commonly used agent; Attruby is overrepresented among newly diagnosed patients

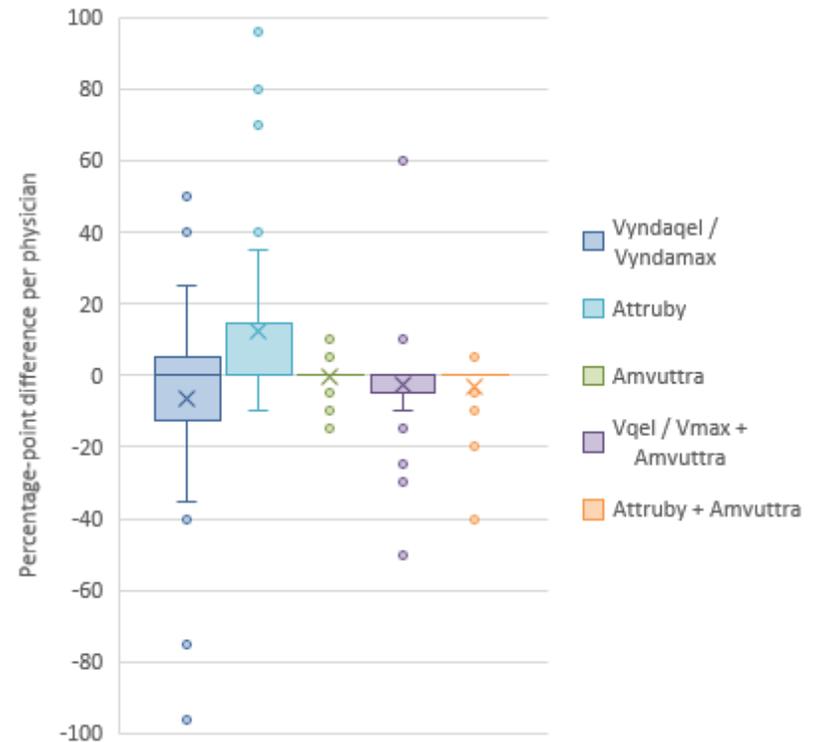
What % of your current ATTR-CM patients are treated with each of the following? (n=30)



Of your newly diagnosed ATTR-CM patients, what % are treated with each of the following as 1L treatment today? (n=30)



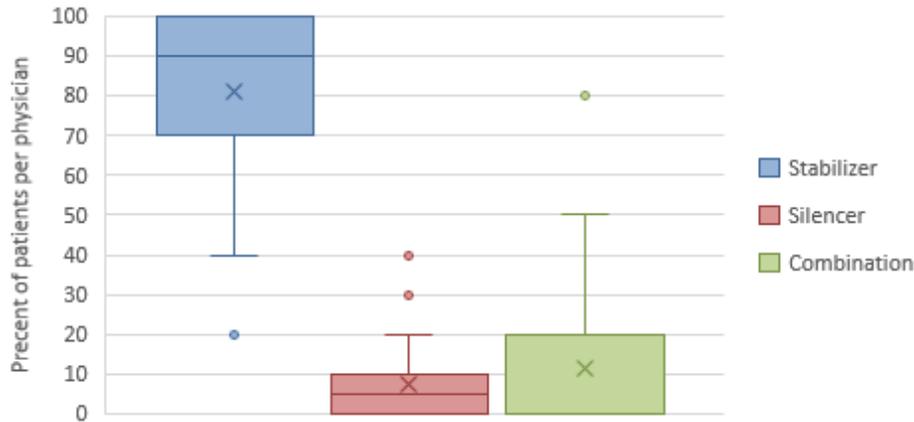
Difference between total ATTR-CM population and 1L treatment (positive difference denotes higher use in 1L)



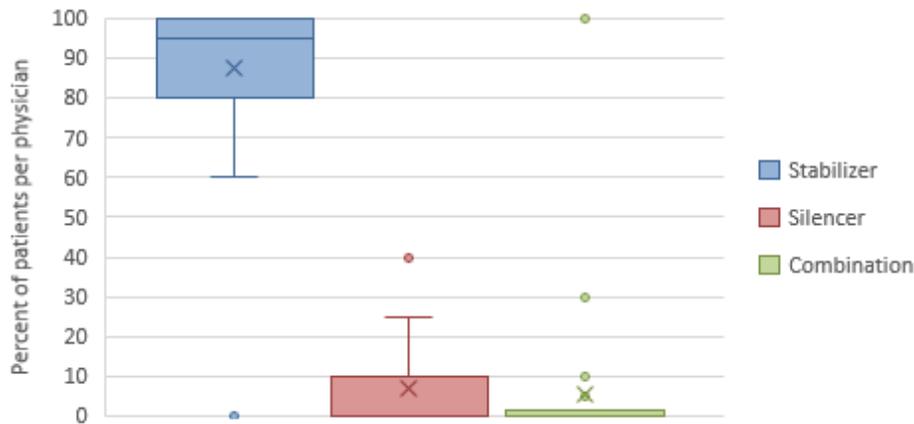
Source: Guggenheim Securities, LLC survey, n=30

Combining agents by class, stabilizers are the most commonly used agent in both overall population and 1L; combination therapy is largely relegated to 2L

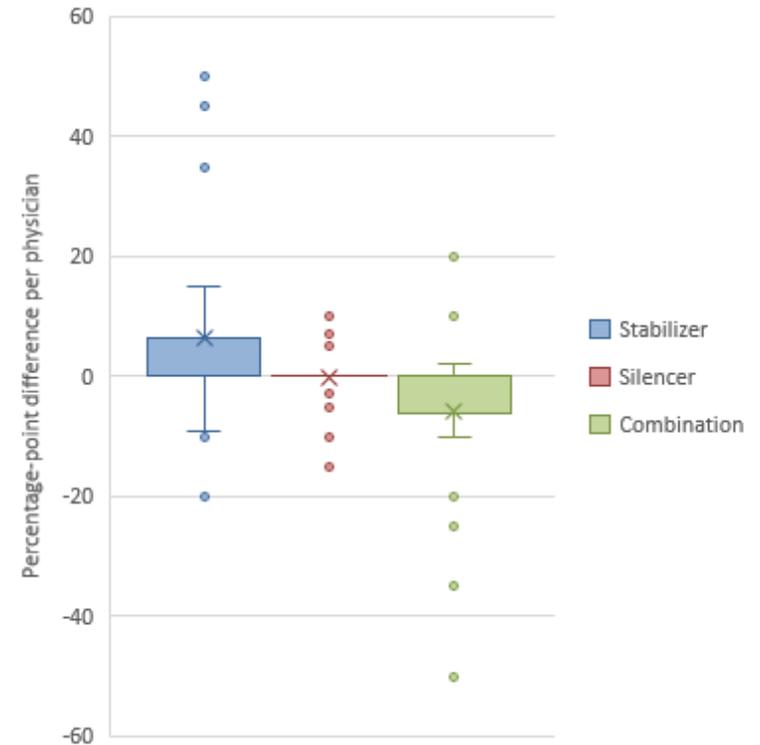
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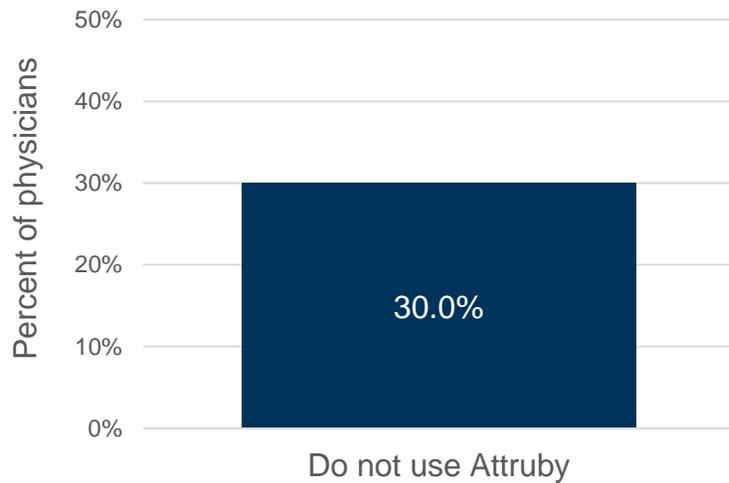
Difference between total ATTR-CM population and 1L treatment (positive difference denotes higher use in 1L)



Source: Guggenheim Securities, LLC survey, n=30

Most physicians not using Attruby or Amvuttra say patients are well controlled on other agents; for Amvuttra, reimbursement hurdles are a close second

You indicated that you currently do NOT treat any ATTR-CM patients with ATTRUBY*. Please briefly elaborate on why. (n=9)

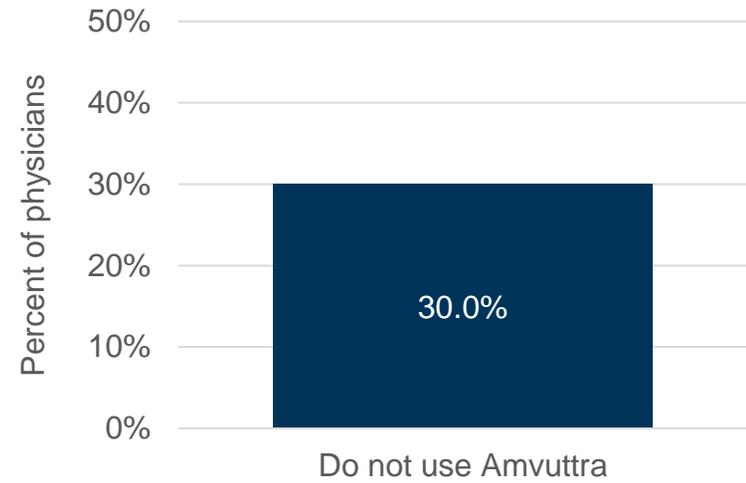


Key reasons stated

1. Patients are well controlled on other agents (n=5)
2. Amvuttra is too new / not enough data to warrant switching (n=4)
3. Reimbursement hurdles (n=2)

Note:* includes ATTRUBY / AVUTTRA monotherapy and combination with other agents
 Source: Guggenheim Securities, LLC survey; n=30 for the overall survey, n=9 applicable to the questions on this slide

You indicated that you currently do NOT treat any ATTR-CM patients with AMVUTTRA*. Please briefly elaborate on why. (n=9)

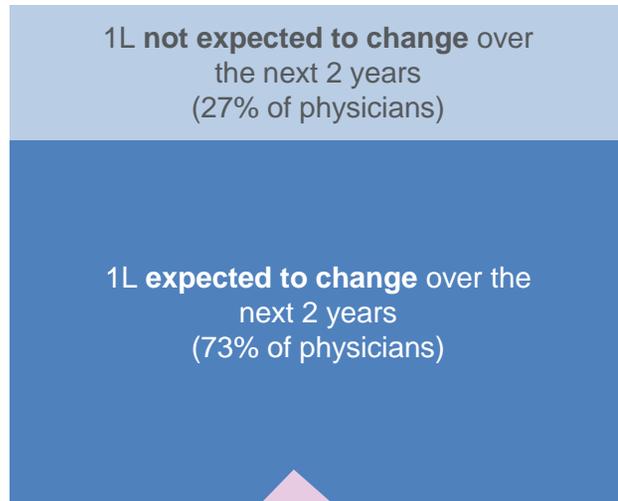


Key reasons stated

1. Patients are well controlled on other agents (n=5)
2. Amvuttra is too new / not enough data to warrant switching (n=1)
3. Reimbursement hurdles (n=4)
4. No relationship with infusion center (n=1)

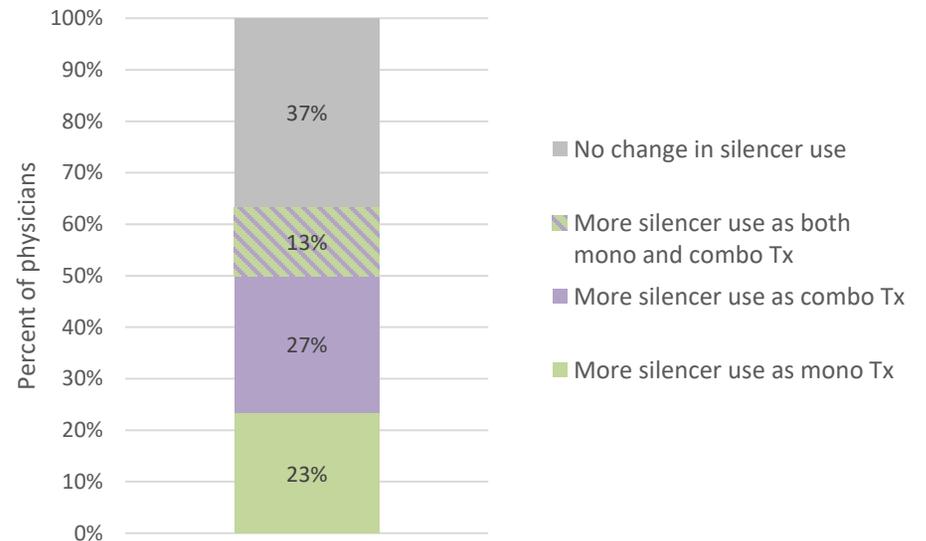
Most cardiologists expect 1L paradigm to shift over the next 2 yrs, with tafamidis monotherapy losing share to Amvuttra and stabilizer + silencer combination

Do you expect new prescription preferences to be meaningfully different 2 years from now, assuming no new treatments are approved for ATTR-CM? (n=30)



10% of physicians do not expect increased silencer use but anticipate shifting from Vqel/Vmax to Attruby

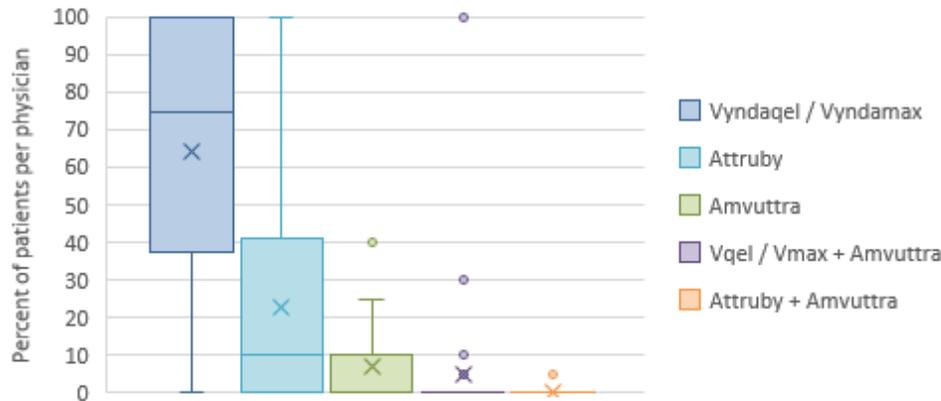
63% of physicians indicate they expect to increase their use of silencers in 1L, either as a monotherapy, in combination with stabilizers, or both. None of the surveyed physicians anticipate a decrease in silencer use. (n=30)



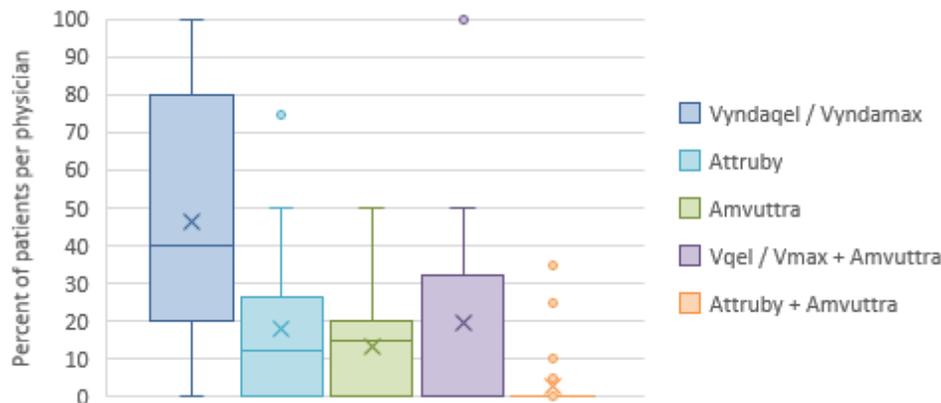
Source: Guggenheim Securities, LLC survey, n=30

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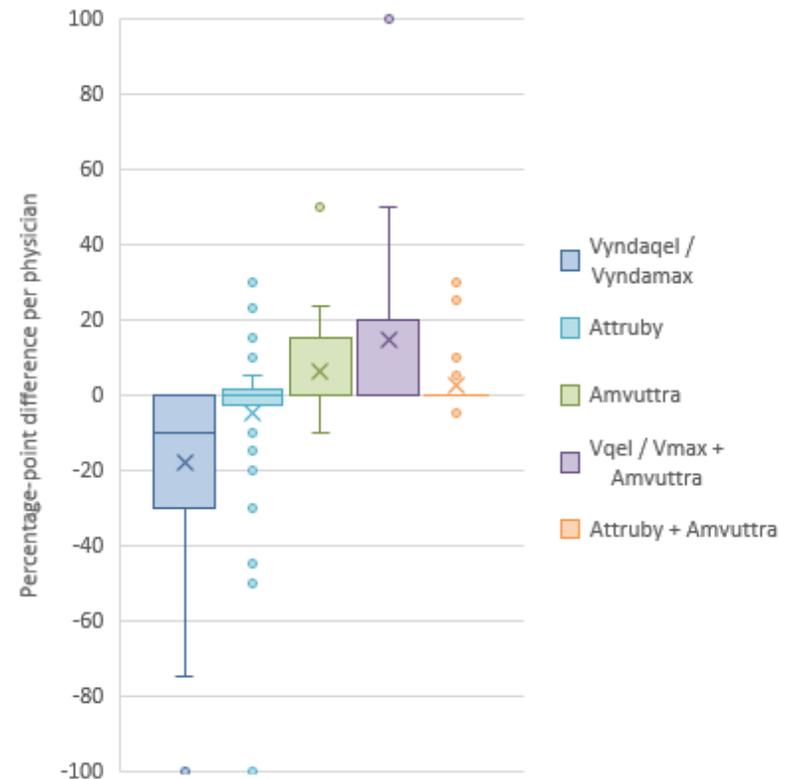
Of your newly diagnosed ATTR-CM patients, what % are treated with each of the following as 1L treatment today? (n=30)



Of your newly diagnosed ATTR-CM patients, what % are treated with each of the following as 1L treatment 2 years from now, assuming no new therapies enter the market? (n=30)



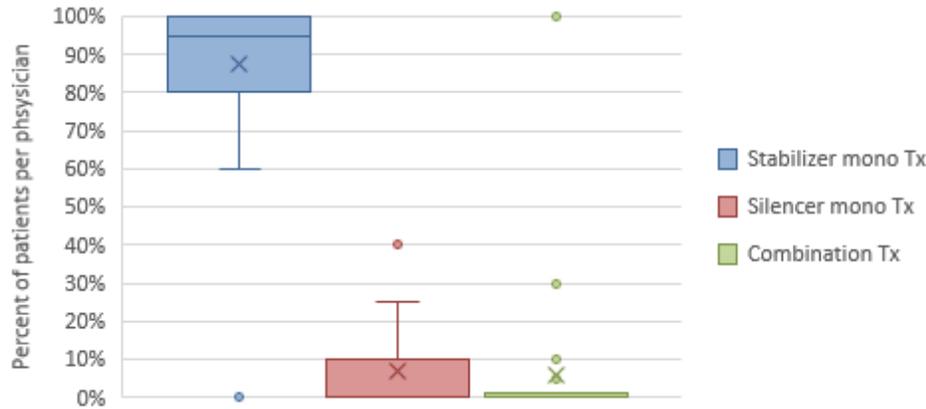
Difference between treatment preference for newly diagnosed ATTR-CM patients 2 years from now compared to today, assuming NO new therapies enter the market by then (positive difference denotes higher use in the future)



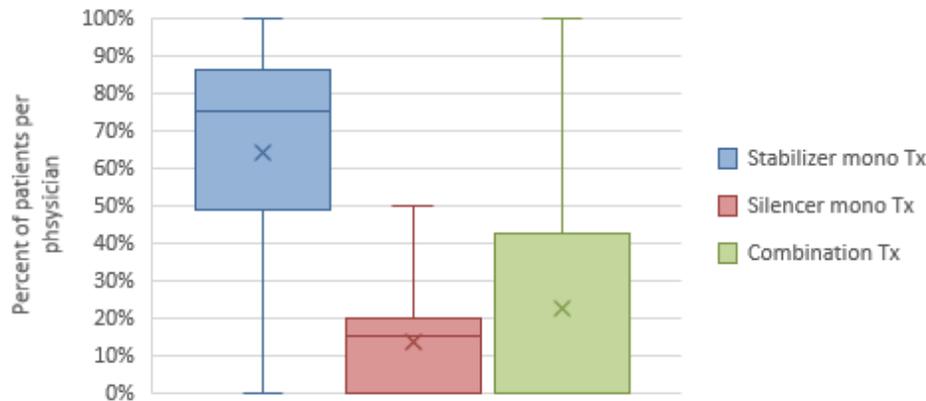
Source: Guggenheim Securities, LLC survey, n=30

Combining agents by class further highlights the expected shift from stabilizer monotherapy towards silencer monotherapy or combinations

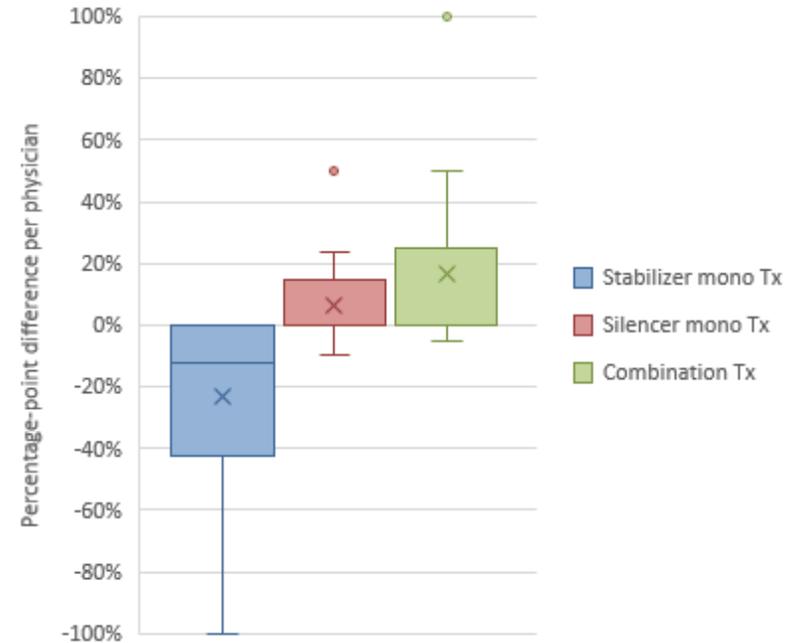
Of your newly diagnosed ATTR-CM patients, what % are treated with each of the following as 1L treatment today? (n=30)



Of your newly diagnosed ATTR-CM patients, what % are treated with each of the following as 1L treatment 2 years from now, assuming no new therapies enter the market? (n=30)



Difference between treatment preference for newly diagnosed ATTR-CM patients 2 years from now compared to today, assuming NO new therapies enter the market by then (positive difference denotes higher use in the future)



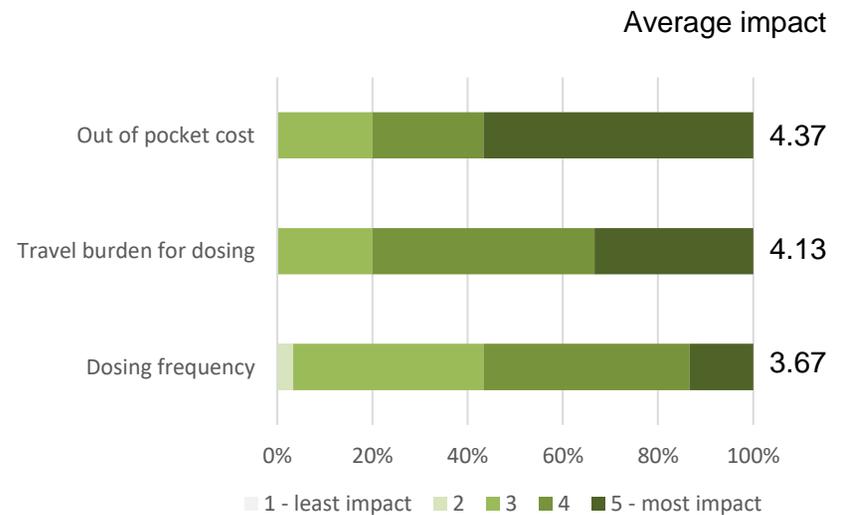
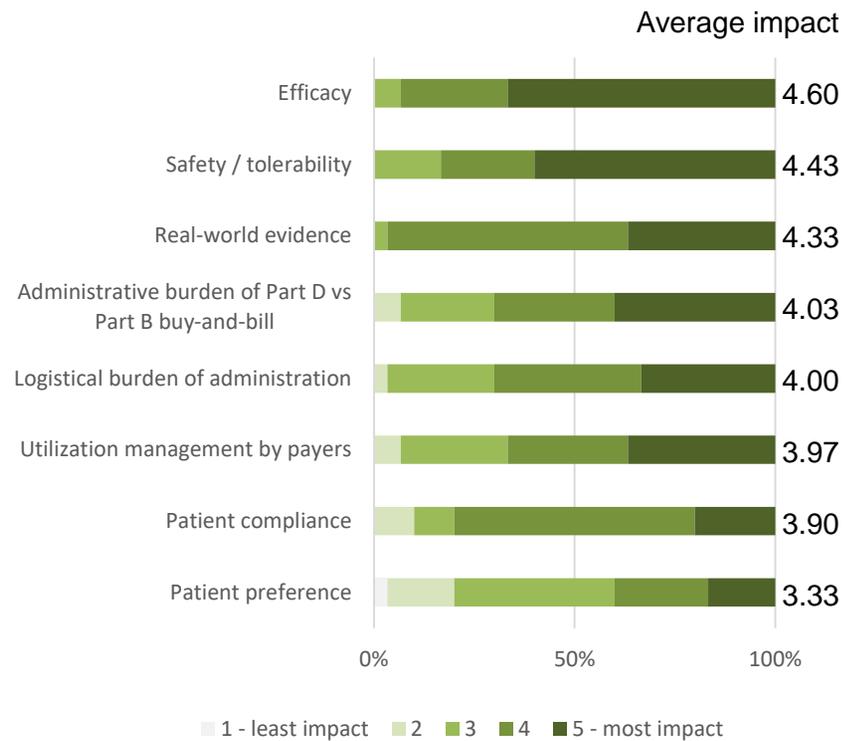
None of the surveyed physicians expect increased use of stabilizer monotherapy in first line

Source: Guggenheim Securities, LLC survey, n=30

Efficacy remains the most impactful criterion for physicians when choosing a first-line treatment

How much impact does each of the following criteria have on your decision in practice when selecting a first-line treatment for a new ATTR-CM patient? (n=30)

How impactful are each of the following criteria in shaping patient preference as the first-line treatment for a new ATTR-CM patient? (n=30)

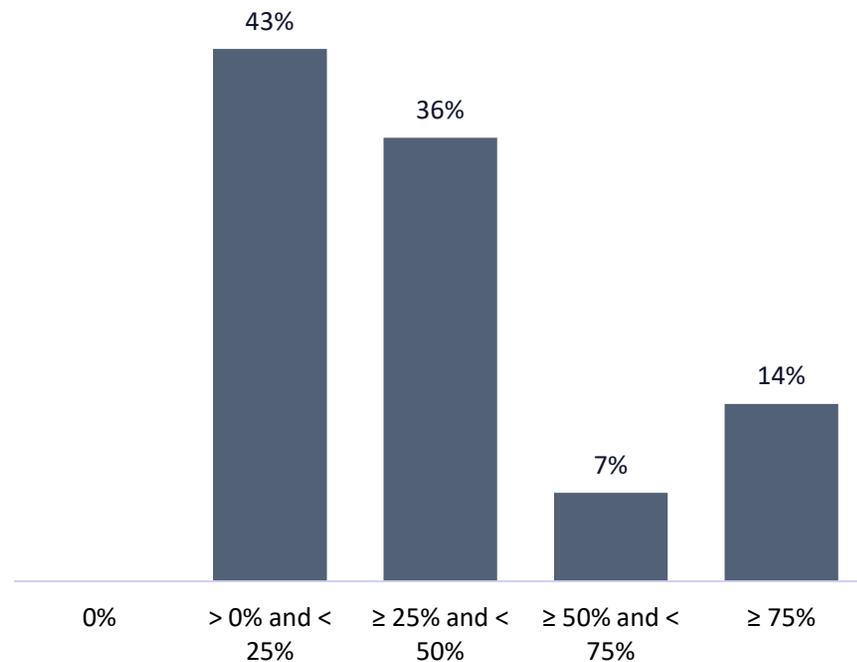


Physicians were instructed to evaluate the impact of these criteria **in practice**, e.g. if all approved treatments had equivalent efficacy, respondents would indicate a low impact on their choice of treatment

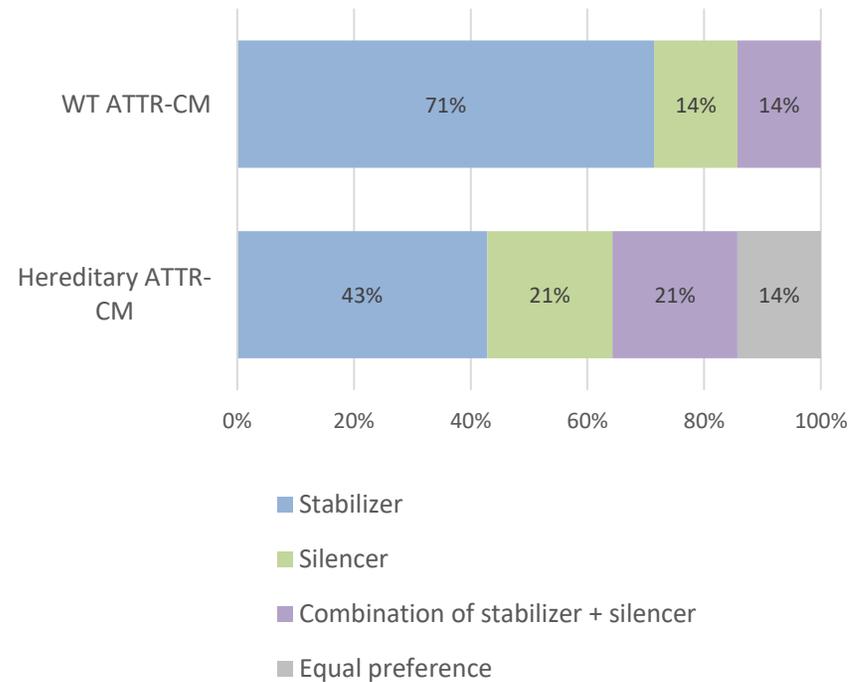
Source: Guggenheim Securities, LLC survey, n=30

Hereditary ATTR-CM patients are less likely to receive stabilizer monotherapy as 1L treatment

What percentage of your newly diagnosed patients that are started on AMVUTTRA are hereditary ATTR patients? (n=14)*



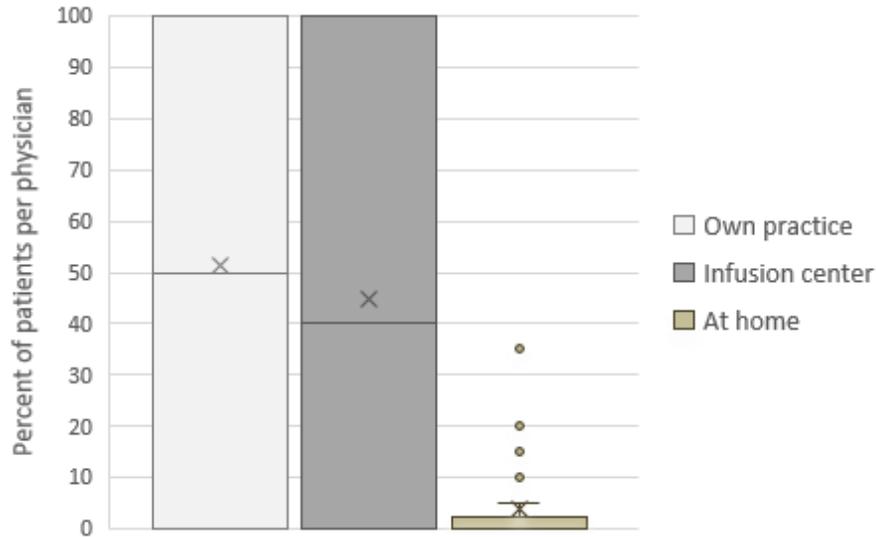
For a newly diagnosed hereditary ATTR-CM / WT ATTR-CM patient, what type of therapy are you most likely to start them on? (n=14)*



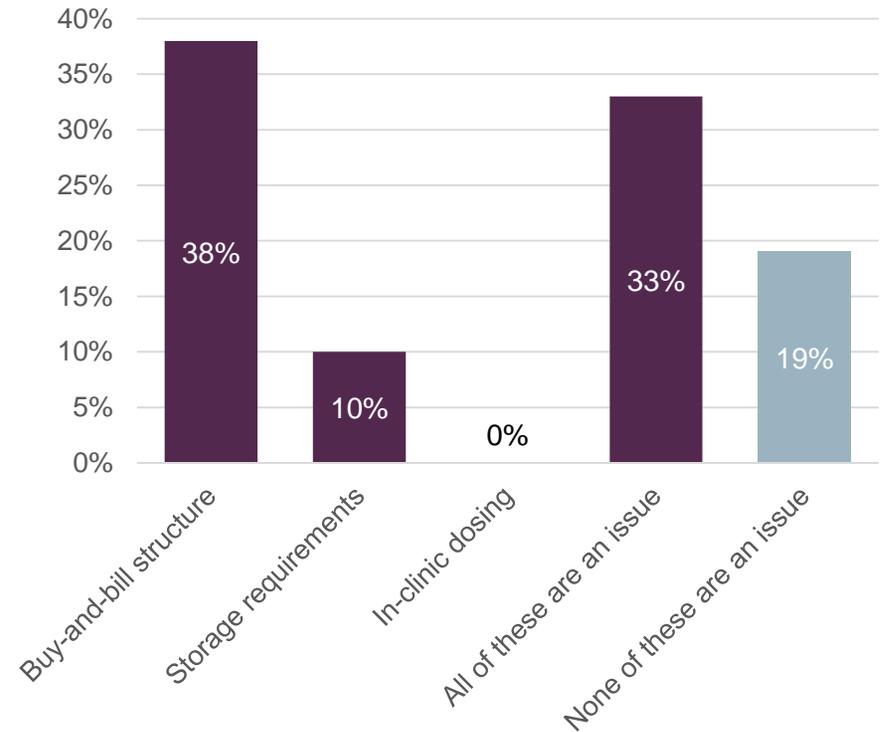
Note:* Only includes physicians that treat some of their newly diagnosed patients with AMVUTTRA
 Source: Guggenheim Securities, LLC survey; n=30 for the overall survey, n=14 applicable to the questions on this slide

Amvuttra administration is spread evenly between prescriber practice and infusion centers; buy-and-bill is the biggest challenge for Amvuttra prescribers

In what setting do your patients receiving AMVUTTRA typically receive maintenance treatment? (n=21)*



What among AMVUTTRA's buy-and-bill structure, in-clinic dosing, and storage requirements is the most difficult parameter to accommodate? (n=21)*

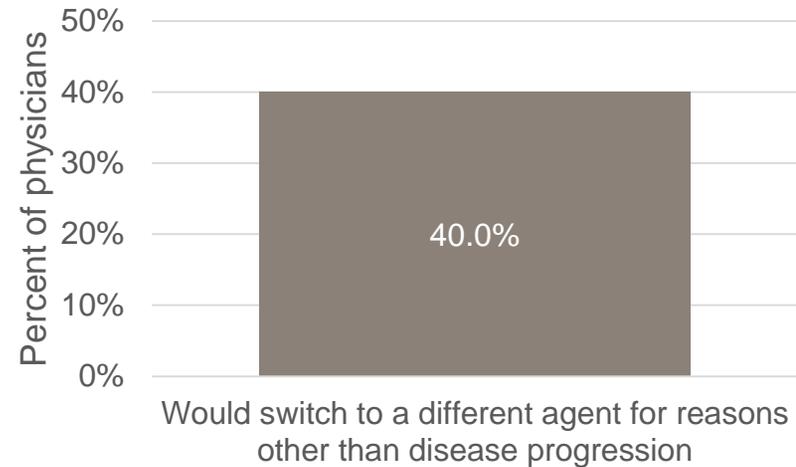
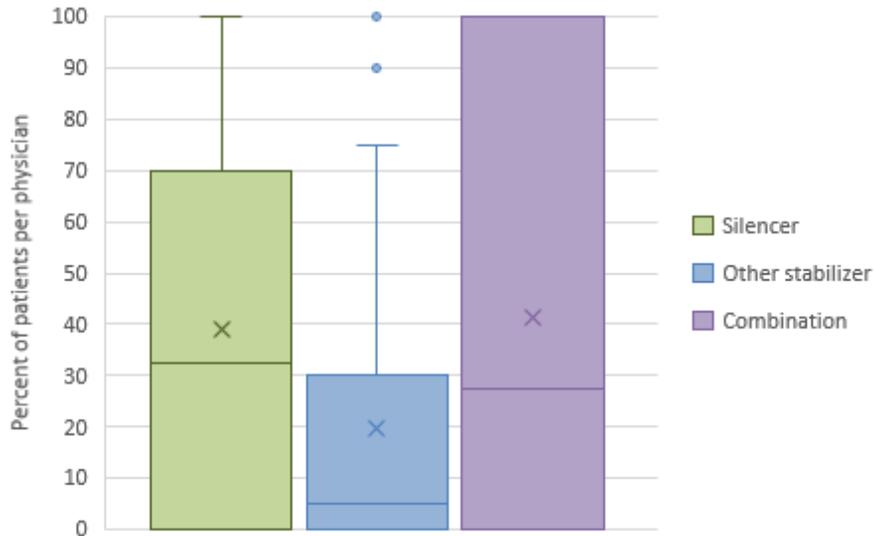


Note:* Only includes physicians that treat some of their patients with AMVUTTRA
 Source: Guggenheim Securities, LLC survey; n=30 for the overall survey, n=21 applicable to the questions on this slide

A majority of physicians use silencer mono- or combo therapy as 2L; besides disease progression, tolerability is the most cited reason for switching agent

For patients that use a stabilizer (VYNDAQEL / VYNDAMAX or ATTRUBY) as first-line treatment and experience disease progression, what do you use as second line therapy? (n=30)

Are there reasons other than disease progression that may trigger a switch to a different agent? (n=30)



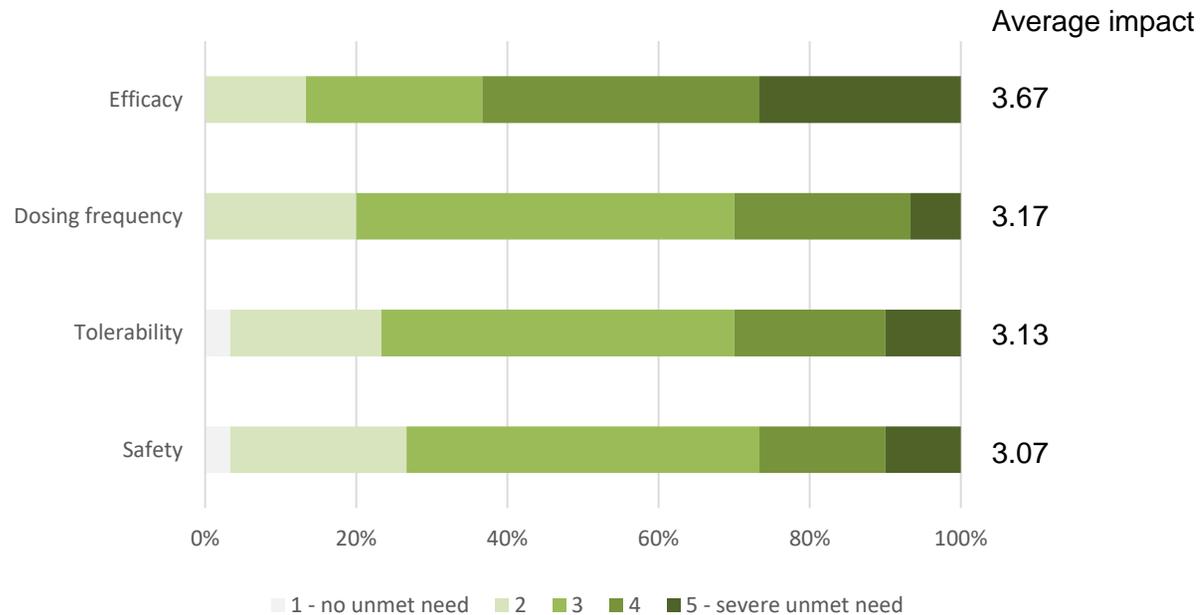
Key reasons stated

1. Side effects / tolerability (n = 7/12)
2. Reimbursement hurdles / OOP cost (n = 5/12)
3. Patient compliance / dosage (n = 4/12)

Source: Guggenheim Securities, LLC survey, n=30

In the eyes of clinicians, efficacy remains the principal unmet need of ATTR-CM patients, indicating room for next-generation agents (e.g., Anylam’s nucesiran)

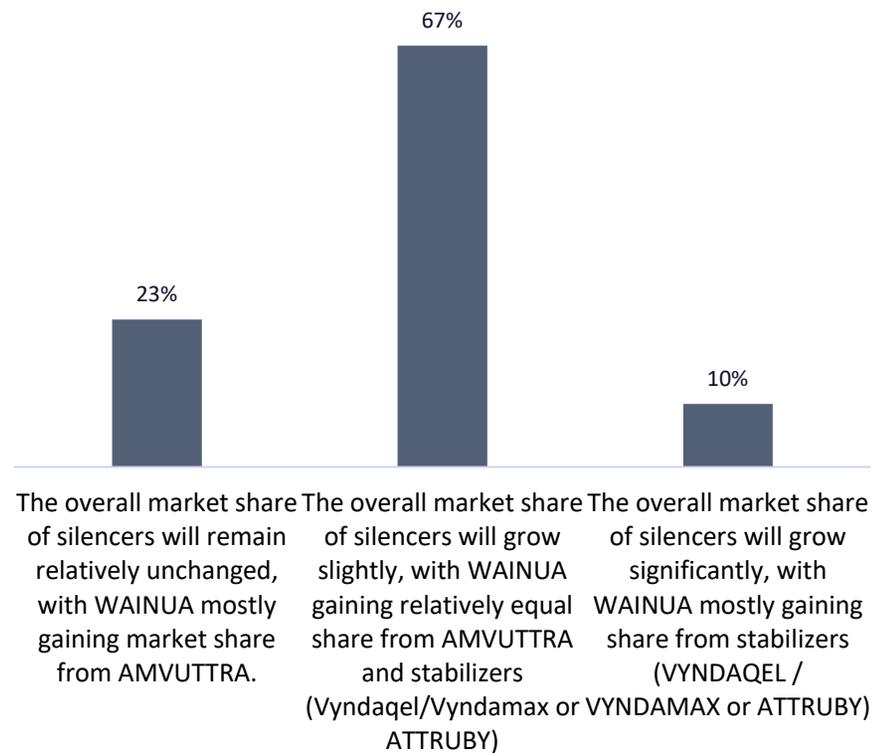
On a 1-5 scale, how much remaining unmet need is there for ATTR-CM that future treatments should address in each of the following? (n=30)



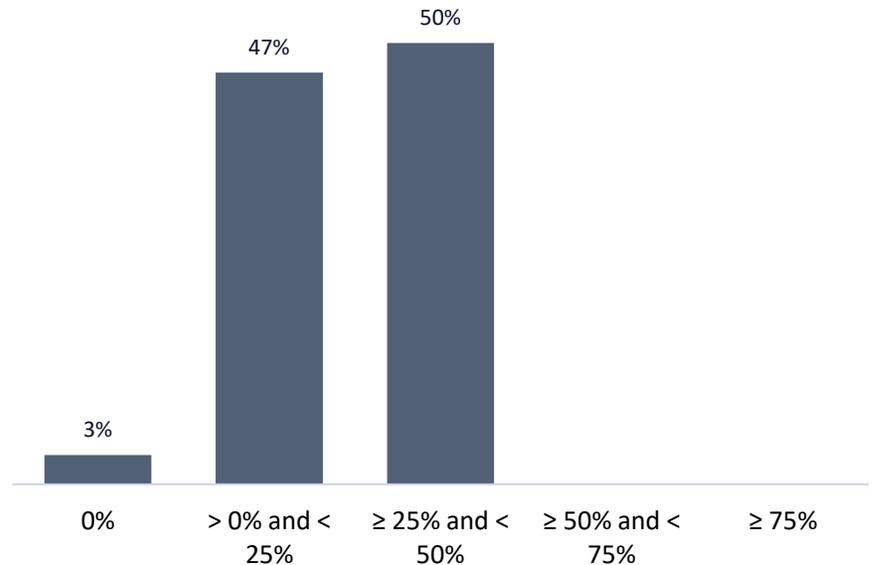
Source: Guggenheim Securities, LLC survey, n=30

Physicians anticipate approval of WAINUA in ATTR-CM to grow the market of silencers in favor of stabilizers but would only switch a minority of patients

Should WAINUA (eplontersen) be approved in ATTR-CM, how do you expect this to affect the overall market share of silencers in ATTR-CM? (n=30)



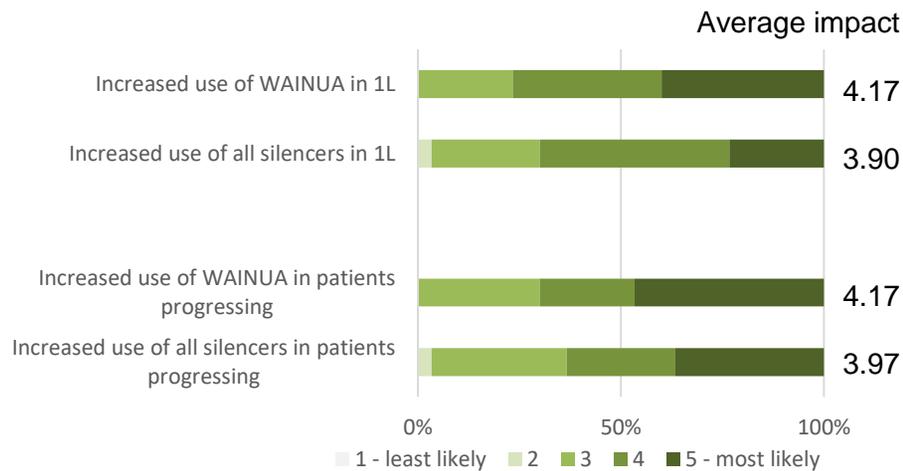
If WAINUA shows comparable efficacy and safety to AMVUTTRA, mindful that WAINUA is a Part D drug targeting monthly self-administration, what portion of patients on AMVUTTRA do you anticipate would want to switch to WAINUA? (n=30)



Source: Guggenheim Securities, LLC survey, n=30

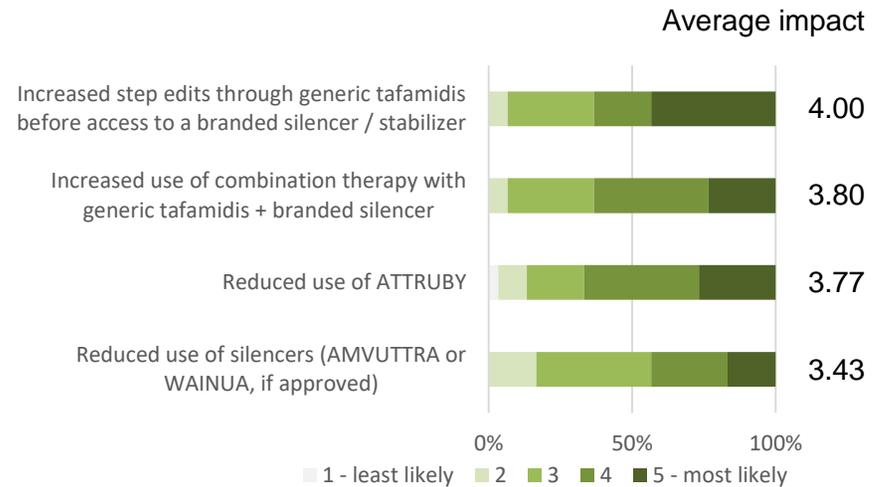
Physicians believe the approval of Wainua is likely to increase the use of silencers; generic tafamidis may promote the use of combination therapy

WAINUA's Ph3 CARDIO-TTRansform trial is designed to evaluate the superiority of WAINUA vs VYND AQEL / VYNDAMAX on mortality and CV outcomes in ATTR-CM. **On a 1-5 scale, how likely do you expect the following situations are for ATTR-CM standard of care if WAINUA successfully demonstrates superiority vs VYND AQEL / VYNDAMAX?(n=30)**



Physicians believe superiority of Wainua vs Vyndamax is likely to have a **positive class effect** on all silencers

On a 1-5 scale, what is the likelihood that the genericization of tafamidis would have the following impacts on the ATTR-CM market? (n=30)



Physicians believe generic tafamidis will likely lead to **more payer restrictions**

Source: Guggenheim Securities, LLC survey, n=30

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