CARDIOVASCULAR

With clot-busting and blood-thinning brands working to establish themselves as successes, the next wave of potentially transformative cardio products is set to hit the market in 2016. But with the huge advances in treatment comes a raft of concerns, among them daunting pricing pressures. **Rebecca Mayer Knutsen** reports

The cardio sector continues to roll out new treatments to keep our blood pumping smoothly, cholesterol at bay and CV risk at a minimum. And as it does, marketers are striving to find a balance between brands already nestled in the market and the highly anticipated wave of cardio products ready to ink invitations to their launch parties.

All eyes are on PCSK9 inhibitors, the new class of cholesterol-lowering agents that comes with big promise and equally big price tags. The monoclonal antibodies are working to establish themselves among a skeptical crowd of payers and providers who question whether there's enough bang for the buck. And then there are the cardiologists—traditionally a loyal bunch, often sticking with the familiar safety and efficacy profiles of proven brands in order to sidestep surprising new side effects.

The approval of a reversal agent for the new generation of blood thinners could address concerns among some doctors with drugs like BI's Pradaxa

Regeneron/Sanofi's Praluent (alirocumab) and Amgen's Repatha (evolocumab) each received an FDA nod for the treatment of high cholesterol during the summer of 2015. By virtue of winning the race to market, Praluent is the current front-runner. Nonetheless, both drugs have garnered excitement and performed well in trials.

New-to-market cardio solutions are coming face-to-face with a pricing rift. "New products are confronting established—and often generic—products with proven outcomes benefits and lower prices," notes David Day, SVP/account director at Triple Threat Communications. "The medical community demands that new products exceed the efficacy and outcomes benefits of established therapies but also justify a higher cost."

Therapeutically, there's a clear role for both older established drugs and innovative medicines, says Jay Edelberg, MD, PhD, head of Sanofi's PCSK9 Development and Launch Unit. "In cholesterol, physicians first prescribe statins and only consider innovative drugs like Praluent if additional lowering of LDL cholesterol is required."

Jeff Berg, SVP/director of client services at AbelsonTaylor, feels that "years of experience with old drugs carry a greater safety profile halo." He indicates the need for new brands to establish a 20% or greater event reduction over current standard of care to give HCPs and payers more comfort.

Clot busters and blood thinners

Decades-old anticoagulant anchor warfarin has faced competition from a steady stream of new products, including Johnson & Johnson/Bayer's Xarelto, Boehringer Ingelheim's Pradaxa, Pfizer/Bristol-Myers Squibb's Eliquis and, most recently, Daiichi Sankyo's Savaysa. A few factors have driven the tremendous growth in the blood-thinner market. Among them: an aging population necessitating more hip and knee replacements that require a period of deep-vein thrombosis prevention and a growing understanding that arrhythmias carry stroke risk.

For those with atrial fibrillation—a known risk factor for stroke—novel oral anticoagulants (NOACs) promise a sunnier solution: namely, a simpler patient-management process. But will the convenience of these drugs outweigh the associated cost issues, effect on renal function and bleeding risk?

NOACs, predicted to net $15.3 billion in worldwide sales by 2018, tout superior safety with fewer food and drug interactions, not to mention no need for constant monitoring. On the flip side, warfarin (marketed as Coumadin and Jantoven) presents physicians with a familiar profile and promises patients a less startling sticker price. "While warfarin's limitations are great, the clinical community has learned to manage the devil they know," explains Chetan Vijayvergiya, PhD, VP/senior medical brand strategist at Publicis LifeBrands Medicus.

Warfarin is feeling the pressure, especially as its one true line of defense begins to slip away. Recognized by physicians for its vitamin K reversal ability, warfarin was trumped by the FDA's approval of Pradaxa's reversal agent and soon-to-be-approved universal Factor Xa agent. Knowing these options exist should provide comfort to the slow NOAC adopters, Berg says.

Although Eliquis's highly anticipated foray into the market was more sizzle than splash, Bristol-Myers Squibb appears to be making headway in the cardio category, specifically in congestive heart failure. BMS is set to acquire Cardioxyl, a company boasting a CHF drug in Phase-II trials.

Although Bristol-Myers Squibb and Sanofi's antiplatelet agent Plavix (clopidogrel) succumbed to patent expiration in 2012, its generic form continues to reign. Plavix set the gold standard for success in the category, with peak annual sales exceeding $9 billion. From Berg's vantage point, Daiichi Sankyo/Eli Lilly's Effient (prasugrel) and AstraZeneca's Brilinta (ticagrelor) haven't caught on the way branded and generic clopidogrel has. That could soon change, as AZ continues to pursue label expansions for its antiplatelet.

Statins and beyond

Statins, which pit the liver against the enzyme responsible for making cholesterol, have long held the standard-treatment belt. Still, new entrants are battling cholesterol in combination with statins and angling to work alone. Some of the mid- and late-stage compounds knocking on the door include Pfizer's PCSK9 inhibitor, Esperion Therapeutics' novel LDL-lowering drug ETC-1002 and Merck's CETP inhibitor anacetrapib (see Clinical Corner, p. 48).

After many starts and stops, the first statin gained approval in 1987 and began the drug class's rise to stardom in the treatment of coronary artery disease. Pfizer's wildly successful Lipitor (atorvastatin), which lost patent protection in 2011, handily earned the distinction of best-selling drug of all time.

Crestor (rosuvastatin), AstraZeneca's best-selling cardio drug, saw its sales dip in 2015, likely a precursor to its patent expiration this year. Aiming to expand its cardio and metabolic portfolios and strategically offset lost Crestor sales, AstraZeneca announced a $2.7 billion acquisition of ZS Pharma. AstraZeneca stands to gain the company's potassium-binding compound ZS-9 for hyperkalemia, now under FDA review.

If approved in coming years, anacetrapib and ETC-1002 would already have a leg up on PCSK9 inhibitors, the first injectables in the sector. In addition to potentially grabbing first-in-class bragging rights, anacetrapib and ETC-1002 offer oral administration.

Finn Partners managing partner Gil Bashe believes the cost/benefit of using PCSK9s and other high-powered cholesterol fighters is clear

TOP 25 CARDIOVASCULAR PRODUCTS

Category leaders, ranked by US sales

Rank	Product	Manufacturer	US sales $ (millions)	Vs. prior 12 mos.	TRx	Vs. prior 12 mos.
1	**Crestor**	**AstraZeneca**	$6,303.9	8.5%	20,483,127	-7.6%
2	**Zetia**	**Merck**	$2,277.8	13.6%	6,700,213	-6.8%
3	**EpiPen 2-Pak**	**Mylan**	$1,155.5	36.1%	2,593,095	3.7%
4	**Benicar**	**Daiichi-Sankyo**	$1,035.4	10.9%	N/A	N/A
5	**Bystolic**	**Forest Laboratories**	$929.2	20.4%	6,071,122	-8.8%
6	**Benicar HCT**	**Daiichi-Sankyo**	$795.0	9.1%	N/A	N/A
7	**Welchol**	**Daiichi-Sankyo**	$743.2	9.0%	1,479,836	-14.5%
8	**Vytorin**	**Merck**	$719.3	-9.0%	2,003,704	-25.9%
9	**Fenofibrate**	**generic**	$681.9	-21.6%	14,215,364	-0.8%
10	**Ranexa**	**Gilead Sciences**	$635.9	14.9%	1,702,983	5.0%
11	**Atorvastatin Calcium**	**generic**	$632.0	-11.1%	90,221,960	16.5%
12	**Lexiscan**	**Astellas**	$574.3	3.2%	N/A	N/A
13	**Omega-3 Acid Ethyl**	**Teva**	$542.2	123.0%	3,392,265	171.1%
14	**Metoprolol Succinate**	**generic**	$541.3	-24.9%	40,518,391	4.1%
15	**EpiPen Jr. 2-Pak**	**Mylan**	$429.7	29.0%	861,733	0.6%
16	**Multaq**	**Sanofi**	$421.2	13.3%	710,318	-9.3%
17	**Pravastatin Sodium**	**generic**	$392.9	-31.2%	32,421,482	-6.3%
18	**Azor**	**Daiichi-Sankyo**	$399.0	5.5%	N/A	N/A
19	**Diovan**	**Novartis**	$337.4	-80.3%	N/A	N/A
20	**Toprol-XL**	**AstraZeneca**	$301.5	33.8%	N/A	N/A
21	**Valsartan**	**generic**	$288.8	-10.3%	8,245,247	324.5%
22	**Adcirca**	**Lung Biotechnology**	$286.7	12.5%	N/A	N/A
23	**Niacin ER**	**generic**	$271.3	-45.5%	2,134,037	-18.4%
24	**Propranolol HCL**	**generic**	$261.9	35.1%	9,962,223	3.9%
25	**Lipitor**	**Pfizer**	$240.5	-11.2%	761,243	-27.5%

Source: IMS Health
Sales data run from October 2014-September 2015.
List includes lipid regulators, anti-hypertensives and other cardiovasculars.

CLINICAL CORNER

In the wake of failures by other contenders in the CETP inhibitor class, Merck is prepping for a long battle. If anacetrapib meets the last leg of clinical trials, the market potential of the last-standing cholesteryl-ester transfer protein (CETP) inhibitor is practically immeasurable.

Developed to increase levels of "good" cholesterol (HDL) and decrease levels of "bad" cholesterol (LDL), Merck's CETP inhibitors need to adapt to focus on the LDL piece at this stage in the game. David Day, SVP/account director at Triple Threat Communications, sees little prospect for a drug that raises HDL, especially given the failure of other forms of HDL-raising drugs (like Abbott's Niaspan) to show outcomes benefits.


Chetan Vijayvergiya

"The Niaspan CV outcomes trial failed to show additional benefit added to statins in some patient types and has damaged the HDL benefit hypothesis," notes AbelsonTaylor SVP/director of client services Jeff Berg. Adds Chetan Vijayvergiya, PhD, VP/senior medical brand strategist at Publicis LifeBrands Medicus, "I'm not sure I can remember a class where the first two agents failed, let alone the first three, and the next one was a success. That being said, perceived concerns of toxicity may impact the potential for anacetrapib."

According to Vijayvergiya, concerns stem from anacetrapib's "accumulation in the body, as drug levels are detected up to 40% at 12 weeks post cessation of therapy." Further, detectable drug levels were found up to four years post-therapy cessation in a small number of patients.

Day, however, sees a glimmer of hope in the size of Merck's Reveal trial—which was almost three times as large as Lilly's Accelerate trial for evacetrapib, the most recent CETP inhibitor to go down in flames.

Vijayvergiya points out that Reveal also enrolled a healthier patient population, which may benefit anacetrapib. The study's Data Monitoring Committee recently completed its planned review, including a futility analysis, and recommended the study continue. "This means patients aren't being exposed to unnecessary risk, efficacy data is not strong enough to stop the trial and the study is not futile in meeting its objectives," he explains.

Pfizer's CETP inhibitor torcetrapib flopped amid safety issues. Lack of efficacy, on the other hand, led to the discontinuation of evacetrapib and Roche's dalcetrapib. According to Berg, a recent interim analysis of anacetrapib didn't show safety signals or lack of efficacy.

Positive news has spurred signs of life for other CETP inhibitors. DalCor may revive development of dalcetrapib and Amgen recently acquired Dezima and its CEPT inhibitor TA-8995, which is ready for Phase III trials. Bristol-Myers Squibb is also in the running via its partnership with Simcere and its CETP inhibitor BMS-795311.

The anacetrapib futility analysis recently added to the protocol will offer an early peek at safety and efficacy trends before data reports out in 2017. "If the findings are solid and the eventual pricing is consistent with value, then Merck will again be a dominant cardiovascular presence," notes Finn Partners managing partner, health, Gil Bashe.

for people with extremely high LDL-C, even after using a statin. With trials like Merck's Zetia (ezetimibe) Improve-It showing improved life expectancy, physicians and payers are open to the second-line drug concept, he says. In combo with Merck's statin med simvastatin, Zetia slashed heart risks by 6.4% in patients with acute coronary syndrome.

PCSK9 inhibitors single out patients with familial hypercholesterolemia, high rates of LDL that statins alone cannot improve and known statin intolerance issues, adding up to a narrow segment of the cardio crowd. Praluent's Odyssey Outcomes trial, expected to conclude in 2017, assesses the drug's potential to reduce cardiovascular outcomes. "In our clinical trials, most patients achieved their LDL cholesterol goals within weeks of commencing therapy," Edelberg says.

Pfizer's third-to-market appearance in that category may not prevent bococizumab from dominating the competition. Some analysts believe it could achieve best-in-class status due to partner Halozyme's promise to improve the efficacy of individual subcutaneous injections and reduce the required dose with its delivery platform.

Looking beyond 2016, Vijayvergiya has his eye on Alnylam's gene-silencing technology with ALN-PCSsc, an RNAi therapeutic targeting PCSK9 that could offer biannual injections and "revolutionize the management of LDL-C for patients and physicians." Day, on the other hand, points to the Medicines Co.'s ALN-PCS as another promising contender. ALN-PCS blocks the PCSK9 gene (PCSK9 inhibitors block the protein) and requires just two annual doses.

Elsewhere in the category, analysts have noted blockbuster potential for both Novartis's new heart failure medication Entresto and Cytokinetics/Amgen's experimental heart failure agent omecamtiv mecarbil. Entresto benefits a treatable population much larger than that of the PCSK9s and shows a significant mortality benefit over standard treatments.

Drug pricing spillover

In the shadow of the Gilead/AbbVie drama of 2014, new cardio drugs are contending with their share of price controversy. Though not on the same scale as the hep.-C price showdown, cardio marketers might glean some knowledge from the ensuing hubbub.

To justify a price premium, marketers need to demonstrate real value to payers within a disease state. Day believes makers of PCSK9s should follow the lead of hep.-C drug developers by "showing the long-term cost benefits of lowering LDL to levels not previously attained."

Determining which agent in a new class of drugs will seize the most market share often comes down to access, explains Vijayvergiya. "Expensive drugs for a chronic condition pose a great financial burden on the healthcare system, creating significant anxiety for the PBMs," he observes. "Companies that can leverage portfolio assets for deep discounts to obtain optimum access will win this battle."

A formulary battle is brewing between Amgen and Regeneron/Sanofi over their PCSK9 inhibitors. Although both companies have brokered deals with Express Scripts, Amgen inked an exclusive deal with CVS/Caremark to offer Repatha as the only PCSK9 on its plan.

Performance-based pricing may become more prevalent. "Novartis is considering giving discounts for Entresto when the desired outcome isn't achieved and collecting a bonus when outcomes targets are exceeded," Day reports. "If Novartis can overcome the many challenges in this type of arrangement, we could see a rising trend in payer negotiations." ■