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EDITORIAL COMMENT

Off Target But on Track to New Strategies to Mitigate Calcific Aortic Valve Disease*

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Approximately 7% of our drugs approved as pharmacotherapy in the United States have no known primary target, and about twice this number have poorly defined mechanisms of action (1). Moreover, chemoinformatics – the combination of chemistry, structural biology, data mining, and computational sciences to define chemical space in present day pharmacology – has revealed that approximately 5% of drugs with well-defined therapeutic targets have high-affinity off-target interactions (2). Off-target molecular interactions molecules may provide either therapeutic benefit or untoward side effects. This drug property, known as polypharmacology, has been well appreciated for years, and on occasion has been clinically useful even when precise mechanisms were initially unclear. For example, the antibiotic demeclocycline arguably found its most unique therapeutic benefit in treatment of the syndrome of inappropriate antidiuretic hormone secretion because of the off-target capacity of demeclocycline to induce mild nephrogenic diabetes insipidus and increase free water excretion. However, polypharmacology can significantly complicate patient management; e.g., the well-known negative side effects of amiodarone on thyroid and pulmonary physiology when deployed to treat life-threatening arrhythmias.

In this issue of *JACC: Basic to Translational Science*, Bowler et al. (3) have innovatively followed through on a chemoinformatic clue that pointed to previously unknown polypharmacology. A prior independent, mass spectrometry-based study recently identified the widely used nonsteroidal anti-inflammatory drug celecoxib as a high-affinity ligand for cadherin 11 (CDH11), also known as osteoblast cadherin (4). Studies from the Merryman lab had previously shown that CDH11 was expressed in valve interstitial cells (VICs), and is a key contributor to VIC-mediated osteogenic mineralization in aortic valves via mechanical modulation of the VIC phenotype. Thus, the investigative team examined porcine aortic VIC-mediated matrix calcification in the presence of celecoxib or dimethyl celecoxib—the latter a methylated congener that also binds CDH11 but does not inhibit cyclooxygenase 2 (Cox2). To the authors' surprise, celcoxib increased, whereas dimethyl celecoxib inhibited, calcified nodule formation in VICs grown under prosclerotic conditions (e.g., transforming growth factor-beta with biaxial mechanical strain) (3).

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Furthermore, celecoxib increased the contractile myofibroblast phenotype of VICs in this relevant culture model. Importantly, aortic valve endothelial cells exhibited little to no procalcific activity or modulation. To further establish the relationship between celecoxib and calcific aortic valve disease (CAVD), the authors queried the Vanderbilt Synthetic Derivative, a powerful de-identified patient database enabling an analysis of celecoxib use and the risk for calcific aortic stenosis (AS) (3). Comparison was made to other nonsteroidal anti-inflammatory drugs such as naproxen or ibuprofen that do not bind CDH11. In the adjusted retrospective analysis, celecoxib use was

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associated with a significant 25% increase in AS risk, whereas no such association was found with naproxen or ibuprofen exposure (3). Thus, celecoxib use emerges as a plausible risk factor for calcific AS, potentially related to mechanisms involving VIC Cox2 inhibition in the setting of CDH11 modulation (3).

Why is this paper from Bowler et al. (3) so significant? There are several important features, but 2 stand out as very helpful to consider, including their implications. Firstly and most saliently, celecoxib emerges as a new member in a handful of widely used drugs associated with the CAVD spectrum in humans. Given the high prevalence of calcific AS in our aging population and the failure of statins to favorably impact CAVD (5), close attention must be paid to clinical observations that potentially offer clues to pathogenesis and prevention. The Multiethnic Study of Atherosclerosis revealed that aminobisphosphonate use for osteoporosis was associated with reduced aortic valve calcification in postmenopausal women (6). Because valve calcium accrual portends CAVD progression to clinically relevant AS (5), this suggests that aminobisphosphonates might mitigate progression, but direct evidence is lacking and potential mechanisms unknown. The Japanese Aortic Stenosis Study identified that warfarin use increased, whereas angiotensin receptor blocker use decreased, calcific AS risk (7). As Bowler et al. (3) newly show, Cox2 inhibition in the setting of concomitant Cdh11 antagonism—as occurs with celecoxib—increases risk for AS. This suggests a protective role for Cox2 in limiting VIC calcification; however, this relationship may differ for those Cox2 inhibitors that do not simultaneously impact both Cox2 and CDH11 pathways; for example, naproxen and ibuprofen. Notably, naproxen and ibuprofen use were not associated with increased calcific AS risk (3). Nevertheless, Cox2 generates a spectrum of bioactive oxylipid metabolites—including proinflammatory and proresolving prostaglandins and lipoxins — and pharmacologic modulation or loss of Cox2 markedly perturbs oxylipid metabolism (8). Moreover, oxidized phospholipids (oxPL) also inhibit Cox2 activity as relevant to calcific AS (9). Biochemical and genetic data have converged to reveal oxPL: lipoprotein(a) [Lp(a)] complexes drive calcific AS via lysophosphatidic acid ligand-receptor interactions (10). An important study by Zheng et al. (11) has recently shown that elevated Lp(a) levels (> 35 mg/dl) not only reflect elevated aortic valve calcifying activity as revealed by fluorodeoxyglucose positron-emission tomography/computed tomography, but also portend clinical calcific AS progression (11). As Gotoh first pointed out (12), Lp(a) conveys risk for aortic valve sclerosis and CAVD beyond low-density lipoprotein cholesterol (13), and Lp(a) does not appear to carry risk for coronary artery calcification similar to low-density lipoprotein cholesterol (14). Thus, given the findings of Bowler et al. (3), patients with elevated Lp(a) might be advised to avoid celecoxib, but this clearly requires further study. Tsimika's lab first demonstrated that Lp(a) is the preferred lipoprotein carrier of oxPL in human plasma — and Lp(a) is absent in most preclinical disease models in the absence of transgenic engineering (reviewed in Tsimika et al. [13]). Therefore, in vivo preclinical studies delineating pathomechanisms of celecoxib and Cox2 inhibition—or therapeutic Cox2 modulation—in CAVD should deploy models from which the contributions of Lp(a):oxPL metabolism can be studied as relevant to human disease. Such models also afford the opportunity to determine how the valve cell mechanobiology regulated by CDH11 interacts with Lp(a):oxPL metabolism in VIC phenotypic modulation.

Secondly, this study indicates the power of chemoinformatics to inform and advance human pharmacology. Uniquely keen insight, team science, institutional infrastructure, and chemoinformatics synergized to identify an untoward AS risk associated with celecoxib use (3); this important result is worrisome given give the prevalence of CAVD in our aging population (5), and deserves further investigation and clinical validation. However, the actions of dimethyl celecoxib — a small-molecule antagonist of CDH11 that avoids Cox2—on limiting VIC calcifying nodule formation and myofibroblastic phenotype (3) indicates that targeting CDH11 is feasible and potentially fruitful as a strategy for mitigating human AS. Indeed, the Merryman lab has shown that a monoclonal antibody targeting CDH11 can ameliorate CAVD and valve tissue stiffness due to murine Notch1 haploinsufficiency (15). These are important observations given the absence of proven pharmacotherapy for human CAVD. Dimethyl celecoxib can serve as a tool compound, enabling refinement of structure-activity relationships in small-molecule modulators of VIC biology via CDH11, potentially useful in AS pharmacotherapy. However, tool compounds have their own shortcomings, and dimethyl celecoxib itself also exhibits polypharmacology, sharing with celecoxib the actions in the cellular endoplasmic reticulum stress response. Studying VIC responses to novel CDH11-targeted small-molecule

inhibitors in development for other indications should prove useful as well. In toto, the enlightening study from Bowler et al. (3) has significant translational implications, providing insight that informs novel strategies to mitigate AS risk in our aging, dysmetabolic population.

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