An economic analysis of aspirin desensitization in aspirin-exacerbated respiratory disease

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Background: Aspirin desensitization is an effective therapy for moderate-to-severe aspirin-exacerbated respiratory disease (AERD). Desensitization also allows the use of aspirin for secondary cardiovascular prevention.
Objective: We sought to investigate the cost-effectiveness of aspirin desensitization with subsequent aspirin therapy in patients with AERD.
Methods: The Healthcare Cost and Utilization Project was used, together with average reimbursements from a large Midwestern health care plan, to model the costs of aspirin desensitization for therapeutic and prophylactic use in patients with AERD. Event probabilities were based on the published literature.
Results: Ambulatory desensitization for AERD cost $6768 per quality-adjusted life year (QALY) saved ($18.54 per additional symptom-free day). Aspirin desensitization for AERD remained cost-effective (<$50,000 per QALY saved) across a wide range of assumptions. When secondary cardiovascular prophylaxis was considered, ambulatory aspirin desensitization was less expensive than an alternative antiplatelet agent, clopidogrel. Clopidogrel cost $106,453 per incremental QALY saved when compared with desensitization.
Conclusions: Aspirin desensitization is a cost-effective therapeutic intervention in patients with moderate-to-severe AERD. Although the incremental cost-effectiveness of clopidogrel in individuals with aspirin allergy is marginal, if available, ambulatory desensitization remains a less-expensive option for secondary cardiovascular prophylaxis.
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Key words: *Cost-effectiveness analysis, quality-adjusted life year, aspirin desensitization, aspirin-exacerbated respiratory disease*

Asthma affects approximately 8% of the general population,[1] and aspirin-exacerbated respiratory disease (AERD) accounts for approximately 21% of adult asthma.[2] AERD (formerly termed the *aspirin triad*) is characterized by aspirin sensitivity, difficult-to-control asthma, and chronic hyperplastic sinusitis with tissue eosinophilia.[2-4] AERD is also associated with increasing asthma severity and airway remodeling.[5] Aspirin desensitization entails the graded administration of aspirin in a controlled setting and has been shown to significantly reduce episodes of acute sinusitis and improve asthma control in patients with AERD.[6-8]

Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
CPT: Current procedural terminology
ICD-9: Internation Classification of Diseases, Ninth Revision
ICER: Incremental cost-effectiveness ratio
NSAID: Nonsteroidal anti-inflammatory drug
QALY: Quality-adjusted life year

Aspirin/nonsteroidal anti-inflammatory drug (NSAID) sensitivity in populations generally distinct from those with AERD might also be characterized by (1) urticaria/angioedema to multiple, structurally distinct cross-reacting NSAIDS (often in association with idiopathic urticaria/angioedema); (2) urticaria/angioedema to a single agent only (presumably based on sensitivity to a structural moiety); or (3) anaphylaxis to a specific agent without cross-reactivity to structurally dissimilar NSAIDS.[9] In patients with specific sensitivity to aspirin or an NSAID, desensitization/challenge procedures (which might differ from those used in AERD) have been used to allow the use of aspirin in patients needing an antiplatelet agent for prevention of secondary vascular events, but these patients represent a distinct population from those with AERD.[9,10] Desensitization is generally unsuccessful in patients with idiopathic urticaria/angioedema who have sensitivity to multiple cross-reacting NSAIDS.

The use of antiplatelet prophylaxis for secondary prevention of subsequent vascular events provides significant protection against subsequent thromboembolic events.[11-13] In patients without aspirin sensitivity requiring secondary cardiovascular prophylaxis, the dramatic differences in cost between aspirin and alternative strategies makes aspirin therapy the more cost-effective choice.[14] Although experience is limited and reactions during desensitization procedures in patients requiring this agent for cardiovascular prophylaxis have been reported, in general patients have tolerated the procedure well[12,13]; however, alternative options are available.[11,15]

Cost-effectiveness analyses are useful in the face of meaningful tradeoffs by providing systematic comparisons of alternative strategies in an explicit and quantitative manner.[16] Such an analysis provides a common metric to compare therapies used in different medical conditions, and benchmarks for cost-effective interventions have been described (therapies costing <$100,000

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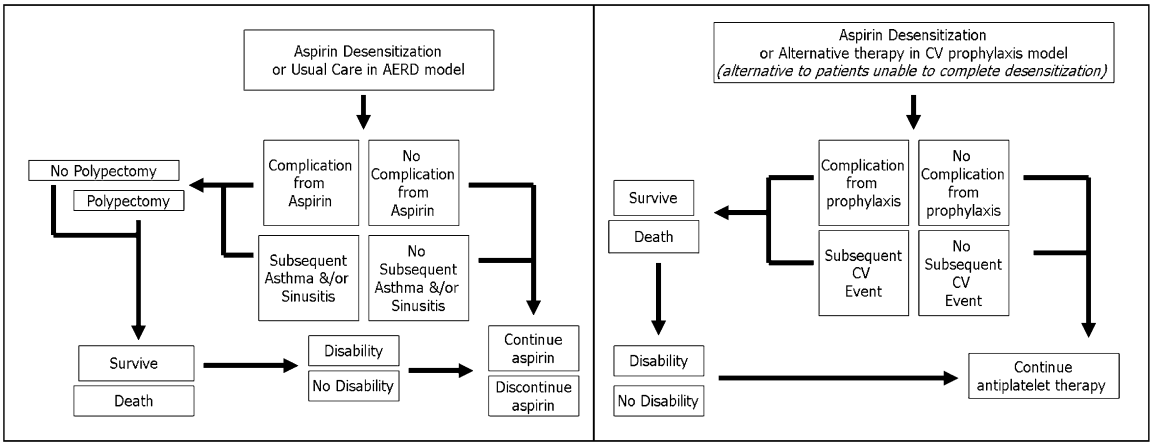

FIG 1. Health states. Health states were defined for patients undergoing therapeutic desensitization for AERD and secondary cardiovascular *(CV)* prophylaxis. Health states belonged to a Markov model with a cycle length of 1 year. In each model cohorts assigned to competing therapies entered the model, and probabilities, costs, and utilities of potential outcomes were applied.

per life year gained are generally considered cost-effective).[17] Because the cost-effectiveness of aspirin desensitization is undefined, we performed an economic analysis of this therapy when used therapeutically for AERD and for secondary cardiovascular prophylaxis in this population.

METHODS

We used a computer-based mathematic model (TreeAge Pro 2005 Suite, Williamstown, Mass) to perform Markov modeling of transitional health states to portray the dynamic nature of risk reduction in the natural history of AERD and secondary cardiovascular prophylaxis. Markov modeling is a decision-analytic model that incorporates a process derived from matrix algebra to describe transitions experienced by a hypothetical cohort of patients between defined health states over a linear timeframe.[16] It is useful in clinical circumstances characterized by recurring probabilistic risk. The incremental cost-effectiveness ratio (ICER) was calculated by dividing the incremental cost difference between aspirin desensitization and the comparator by the incremental effectiveness difference. In the therapeutic model the comparator was usual therapy. In the secondary cardiovascular prophylaxis model the 2 comparators used were nonintervention and alternative therapy:

$$\frac{Cost_{(ASA\ desensitization)} - Cost_{(Comparator)}}{Effectiveness_{(ASA\ desensitization)} - Effectiveness_{(Comparator)}}.$$

We examined competing strategies offered to patients with AERD and created separate models for each indication. Because aspirin can be used for distinct purposes (therapeutic or prophylactic desensitization), the models incorporated societal costs and benefits of health states unique to each indication. Repeat desensitization procedures were not modeled to create models that would be relevant yet parsimonious. The competing strategies compared for the AERD cohorts included the usual therapies for persistent asthma and chronic rhinosinusitis[18-21] used with or without desensitization. In secondary cardiovascular prophylaxis the incremental cost-effectiveness values of aspirin desensitization and clopidogrel (usual alternative therapy) were compared with a common baseline of nonintervention and with each other. Health states (Fig 1) were modeled during the course of desensitization/challenge and subsequent therapy in each of these aspirin-sensitive conditions.

Costs were represented from a societal perspective (Table I)[18,22] by using inpatient charges abstracted from the 2003 Healthcare Utilization Project Nationwide Inpatient Sample[22] and average reimbursements from medical claims data, including all individuals enrolled in a large Midwestern health care plan. After approval by local institutional review boards, reimbursement for specific International Classification of Diseases, Ninth Revision (ICD-9) codes representing costs associated with desensitization were abstracted from all claims for medical services between January 1, 2002, and June 30, 2006 (n = 2,000,000). Costs and utilities were discounted equally at 3% per annum to reflect the average annual consumer price index for all goods and services.[23] Probabilities, costs, and utilities were applied as patients entered the treatment arms of each model. Nondisabled and disabled health states were persistent, and complications (associated with adverse events from therapies or acute events) and interventions (ie, surgical intervention for refractory sinusitis in the AERD model) were transient, leading to

TABLE I. Utilization and medication costs

Costs	Code	n	Mean costs
Utilization costs			
Hospitalization*			
Acute myocardial infarction	ICD-9 410.x	764,133	$13,970
Gastrointestinal hemorrhage	ICD-9 578.x	340,480	$6834
Asthma	ICD-9 493.x	404,483	$4314
Polypectomy	ICD-9 471.0	169	$5931
Ambulatory costs†			
Office visit	CPT 99214	628,550	$75.13
Spirometry	CPT 94070	1644	$195.28
Desensitization	CPT 95180	39	$243.05
Medications‡			
Clopidogrel (1 mo)			$98
Aspirin (1 mo)			$1.25
Fluticasone, 500 μg/salmeterol, 50 μg inhaled (1 mo)			$218
Mometasone nasal (1 mo)			$78
Montelukast, 10 mg (1 mo)			$90
Amoxicillin/clavulanate (2 wk)			$200

*Weighted national estimates of charges as principle diagnosis from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample, 2003, Agency for Healthcare Research and Quality (AHRQ), based on data collected by individual states and provided to the AHRQ by the states.[22]

†Analysis of medical claims data including all individuals enrolled in a large Midwestern health care plan that sought medical services between January 1, 2002, and June 30, 2006.

‡Costs from Drugstore.com online pharmacy.[18]

TABLE II. Model parameters

AERD therapeutic model		CV prophylaxis model	
Variable	**Baseline value**	**Variable**	**Baseline value**
Costs		Costs	
Aspirin desensitization		Aspirin desensitization	
Ambulatory	$1000	Ambulatory	$1000
Inpatient	$10,000	Inpatient	$10,000
Maintenance aspirin therapy[18]	$15	Maintenance aspirin therapy[18]	$15
Asthma hospitalization[22]	$4000	Alternative therapy (annual)[18]	$1175
Polypectomy[22]	$6000	CV event[22]	$14,000
Major complication[22]	$7000	Major complication[22]	$7000
Office visit (local)	$75	Office visit (local)	$75
Disability (annual)[23]	$16,000	Disability (annual)[23]	$16,000
Probabilities		Probabilities	
Desensitization completion[7]	99%	Successful desensitization[7]	99%
Desensitization fatality	<1%	Desensitization fatality	<1%
Risk reduction, asthma exacerbations[7]	20%	CHD risk without antiplatelet[11]	8.6%
Risk reduction, sinus exacerbations[7]	60%	CHD risk with aspirin[11]	6.8%
Probability of nonresponder[7]	12.5%	CHD risk with clopidogrel[11]	6.7%
Probability of sinus surgery (annual)[7]	20%	Mortality risk reduction of antiplatet[11]	15%
Hospitalization, asthma exacerbation[26]	20%	Complications from antiplatelet[29]	10%
Death/disability from complication	<1%	Major complication from antiplatelet*	0.1%; 0.3%
Annual probability of discontinuation[7]		Mortality from CV event[11]	50%
First year	26%	Disability after CV event[28]	50%
Subsequent years (assumed)		Mortality from major complication[29]	2%
Effective, second year	8%	Disability from major complication[28]	50%
Effective, subsequent years	0%	Discount rate	3%
Not effective	30%	Start age (y)	50
Complications[7]			
Major	1% per annum	Health state utilities	
Minor	5% per annum	Disutility from major event[32]	−0.5
	11% first year	Disutility of a minor complication	0
Mortality from major complication[29]	2%	Utility of a disabled health state[31]	0.8
Disability from major complication[28]	50%		
Asthma exacerbation per year	3		
Sinus exacerbations per year	3		
Discount rate	3%		
Start age (y)	30		
Health state utilities			
Utility of AERD[31]	0.9		
Health state utility change in AERD[31]	0.05		
Disutility of major event[32]	−0.5		
Disutility of a minor complication	0		
Disutility of exacerbation	−0.05		
Utility of a disabled health state[31]	0.8		

CV, Cardiovascular; *CHD*, coronary heart disease.
*First 20 years; subsequent years.

disability, nondisability, or death (absorptive health state). Disability costs were estimated by using average hourly earnings for nonsupervisory workers on private nonfarm payrolls (equal to 50% gross earnings).[23] Age-adjusted mortality was assumed by using probabilities derived from the US 2002 life table.[24] Each model required descriptions of health states that might demonstrate variability between patients with differing comorbidities and presentations. Sensitivity analyses were performed on all variables to account for such uncertainties.

Therapeutic model

A hypothetical cohort of 30-year-old patients with AERD was randomized to ambulatory aspirin desensitization or usual care for asthma with chronic sinusitis. The base case was represented by a patient with moderate-to-severe AERD using daily intranasal steroid therapy, inhaled corticosteroid, a long-acting β-agonist, and a leukotriene modifier who experienced 3 episodes of acute sinusitis and 3 asthma exacerbations each year. Expected improvements in asthma control and chronic rhinosinusitis included reductions in exacerbations of asthma and sinusitis. Such benefits of aspirin desensitization were estimated from published trials of aspirin desensitization for AERD.[6,7]

Annual costs of AERD therapies were derived from utilization cost estimates and costs of medications from an online pharmacy (Table I).[18] The average cost of an exacerbation of sinusitis was estimated by using costs of ambulatory care (outpatient visit, current procedural terminology [CPT] 99214, $75) and costs of a 14-day antibiotic course.[18,25] The average cost of treatment of an asthma exacerbation was estimated by using ambulatory costs (outpatient visit, CPT 99214, $75), costs of hospitalization based on data from

TABLE III. Cost-effectiveness of aspirin desensitization and alternative therapies

Strategy	Cost	Δ Cost	Effectiveness*	Δ Effectiveness*	C/E	ICER 1†	ICER 2‡
Therapeutic model							
None	$227,695	—	20.31	—	$11,209	—	—
Desensitization, ambulatory	$232,507	$4812	21.03	0.71	$11,059	$6768	—
Desensitization, inpatient	$241,498	$13,803	21.03	0.71	$11,486	$19,413	—
Secondary CV model							
No antiplatelet	$49,329	—	10.60	—	$4653	—	—
ASA, no allergy	$54,563	$5234	12.47	1.87	$4374	$2796	$119,433
ASA desensitization							
Ambulatory	$55,147	$5818	12.46	1.86	$4425	$3125	$106,453
Inpatient	$59,647	$10,318	12.46	1.86	$4786	$5541	$73,606
Alternative therapies	$69,731	$20,402	12.60	2.00	$5534	$10,206	—

C/E, Cost-effectiveness; *CV*, cardiovascular; *ASA*, aspirin.
*Effectiveness adjusted for quality of life (health state utilities) and expressed as QALY.
†The first ICER was calculated by using the incremental cost and effectiveness between aspirin desensitization and usual therapy (AERD) or nonintervention (secondary cardiovascular prophylaxis model).
‡The second ICER was also calculated by using the incremental cost and effectiveness between clopidogrel and aspirin desensitization for the secondary cardiovascular prophylaxis model.

the Health Care Utilization Project (ICD-9 493.x, $4314),[22] and the probability of hospitalization during an asthma exacerbation (20%).[26] Costs of minor complications were based on costs of ambulatory care (outpatient visit, CPT 99214, $75), and major complications were modeled from the Health Care and Utilization Project (gastrointestinal hemorrhage, ICD-9 578.x, $6834). The cost of ambulatory desensitization was modeled at $1000 by using reimbursed charges (2 average outpatient visits [CPT 99214, $150], desensitization on 2 consecutive days [CPT 95180, $486], and spirometric measurements during the course of desensitization [CPT 94070, $390]). A desensitization completion rate of 99% was modeled.[7] The rate of polypectomy assumed was 0.2 per year.[7] Patients experiencing successful aspirin desensitization assumed a 60% risk reduction in sinusitis and a 20% risk reduction in acute asthma exacerbations.[7] Additional assumptions were derived from the work of Berges-Gimeno et al (Table II).[7]

Secondary cardiovascular prevention model

Patients with AERD entered the hypothetical trial at 50 years of age and received either clopidogrel or aspirin desensitization for secondary cardiovascular prophylaxis. Baseline assumptions for these cohorts are shown in Table II. The probability of successful desensitization and risks of procedural complications, therapeutic complications, and subsequent vascular events were applied to hypothetical subjects entering this model. Well-controlled studies of aspirin desensitization for this indication are scarce, but when attempted, desensitization/challenge procedures can be successful in a selected patient population.[12,13,27] A desensitization completion rate of 99% was modeled.[7] Because of the number of procedures performed for this indication, procedural mortality, although not reported, is uncertain. We applied a 0.1% ceiling estimate of procedural mortality from desensitization as an upper limit.

The base case was represented by a patient with a previous myocardial infarction. Cardiovascular risk was based on the Antithrombotic Trialists' "Collaborative meta-analysis of randomized trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high-risk patients."[11] In this analysis the baseline risk of nonfatal reinfarction without antiplatelet therapy over a period of 2 years was 6.5% (654 events/10,022 patients). Nonfatal stroke was observed in 129 (1.4%) subjects, whereas vascular deaths occurred in 939 (9.4%) subjects. The combined annual risk of vascular events was 8.6%, and approximately half of these repeat vascular events were fatal. Antiplatelet therapy was associated with a 20.6% risk reduction in subsequent cardiovascular events, and clopidogrel reduced serious vascular events by 10% compared with aspirin. Antiplatelet therapies were also associated with a 15% proportional reduction in vascular and nonvascular deaths.[11] Half of the survivors of a subsequent cardiovascular event were assumed to have some degree of disability,[28] and disability costs were estimated by using average hourly earnings for nonsupervisory workers on private nonfarm payrolls (equal to 50% gross earnings).[23] Equivalent disability rates were assumed for patients with recurrent vascular events and major therapeutic complications. Each of these antiplatelet agents also carries risks of therapeutic complications, such as gastrointestinal hemorrhage or stroke, and these risks were modeled to increase proportionately with age to reflect the literature on the natural history of these complications.[11] The risk of a major complication was estimated at 0.1% per annum for the first 20 years of therapy and 0.3% per annum thereafter. Minor complications occurred in 10% of patients.[29] Costs of major complications were estimated from the Health Care and Utilization Project (acute myocardial infarction, ICD-9 410.x, $13,970; gastrointestinal hemorrhage, ICD-9, $6834). Costs of minor complications were based on local reimbursements (outpatient visit, CPT 99214, $75). Costs of maintenance therapy with aspirin or clopidogrel were estimated from the average commercial price of commonly used medications (Table I).[18] Health state utilities and disutilities for chronic disease were estimated from the published literature.[30-32]

Sensitivity analyses

Inpatient aspirin desensitization was modeled in sensitivity analyses. We used the average costs of more acute conditions abstracted from the Health Care Utilization Project to estimate an upper limit of inpatient desensitization (acute myocardial infarction, ICD-9 410.x, $13,970; gastrointestinal hemorrhage, ICD-9, $6834). Additional sensitivity analyses were performed by using a computerized iterative process to determine critical variable inputs associated with a change in cost-effectiveness (threshold cost-effectiveness values).

RESULTS

In patients with AERD, ambulatory desensitization was found to be cost-effective in the prevention of disease exacerbations and the need for surgical intervention in chronic hyperplastic sinusitis (Table III). Savings associated with fewer exacerbations of asthma and sinusitis economically favored aspirin desensitization. Desensitization cost $6768 per quality-adjusted life year (QALY) gained ($18.54 per additional symptom-free day).

The therapy remained cost-effective across a wide range of assumptions (Figure 2), including the baseline number of asthma or sinus exacerbations, risk reduction afforded by the therapy, setting of the desensitization procedure, and rate of discontinuation. Aspirin desensitization remained cost-effective compared with usual care when inpatient costs were modeled ($19,413 per QALY saved, desensitization vs usual care).

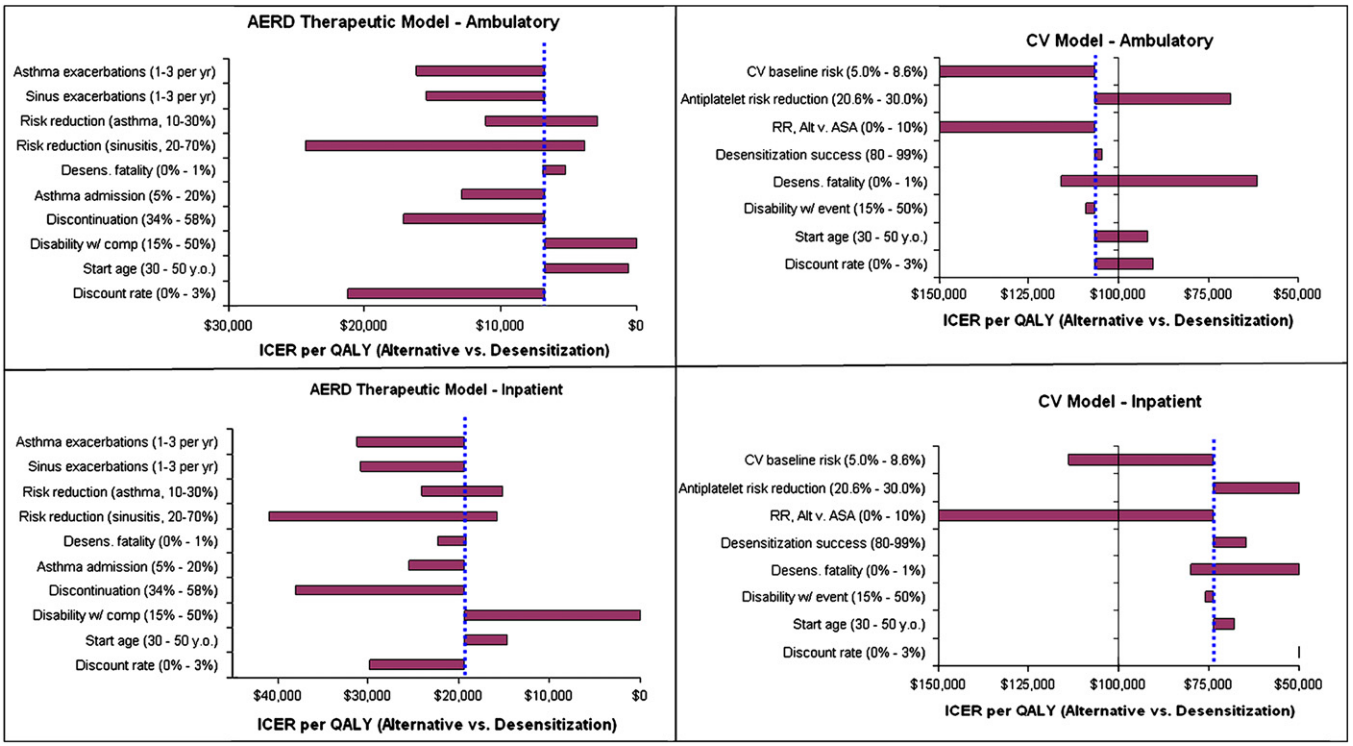

FIG 2. Sensitivity analyses. The *dashed line* represents base-case ICERs for each scenario. In the AERD therapeutic model (ICER for desensitization vs usual therapy), aspirin (*ASA*) desensitization was cost-effective across a wide range of assumptions. In the secondary cardiovascular (*CV*) prophylaxis model (ICER for the alternative agent clopidogrel vs desensitization), a threshold of cost-effective medical care is indicated by the *hatched line* at $100,000 per QALY. Although aspirin desensitization was less expensive, clopidogrel (alternative therapy) was marginally cost-effective.

With regard to prevention of secondary cardiovascular events in high-risk patients, desensitization was less expensive than alternative therapy; however, clopidogrel was marginally cost-effective when compared with desensitization (Table III). Ambulatory desensitization for secondary cardiovascular prophylaxis cost $3125 per QALY saved compared with $10,206 per QALY saved for alternative therapy. Compared with desensitization, the incremental cost of alternative therapy was $106,453 per QALY saved.

The incremental cost-effectiveness of therapeutic aspirin desensitization was robust across a wide array of assumptions, remaining less than $50,000 per QALY saved. The incremental cost-effectiveness of aspirin over clopidogrel was sensitive to baseline cardiovascular risk, degree of risk reduction afforded by antiplatelet therapies, procedural risk, setting of desensitization, and patient age (Fig 2).

DISCUSSION

Aspirin desensitization is a cost-effective intervention for moderate-to-severe AERD ($6768 per QALY saved). As the severity of hyperplastic sinusitis and inflammatory asthma associated with AERD increases, desensitization becomes increasingly cost-effective. When compared with aspirin desensitization in patients requiring secondary cardiovascular prophylaxis, alternative antiplatelet therapy is more expensive but marginally cost-effective (ICER $106,453).

Asthma produces a significant effect on economic resources and quality of life, and evidence suggests that patients might be willing to pay, on average, between $200 and $350 per month for an asthma cure.[30,33] Therapeutic aspirin desensitization provides significant improvements in patient outcomes.[6,7] Our analysis demonstrates that desensitization is a cost-effective intervention in many clinical circumstances.

Because aspirin desensitization might be indicated in patients requiring secondary cardiovascular prevention, we also studied the cost-effectiveness of a competing antiplatelet agent. Such circumstances are characterized to a greater degree by clinical uncertainty and a tradeoff between immediate and future risks associated with significant morbidity and mortality. Previous work suggests that the routine use of clopidogrel for secondary cardiovascular prophylaxis in a population without aspirin allergy is not particularly cost-effective. Gaspoz et al[14] demonstrated that such an approach would cost at least $130,000 per QALY saved. The incremental cost-effectiveness of aspirin is driven by the high cost of alternative medications. When our model was applied to a cohort without aspirin allergy, the ICER identified was similar to that reported by Gaspoz et al ($119,433 per QALY saved). The slight difference in the ICER between the current study and previous work likely relates to variation in modeling techniques. However, when additional costs associated with aspirin desensitization were considered, the economic advantage of aspirin to clopidogrel is less pronounced. As such, it appears that in the population with aspirin allergy, either approach might be reasonable, although desensitization would be less expensive.

There are several limitations to our study. The models assumed ambulatory desensitization procedures. Ambulatory aspirin desensitization is used in many centers for patients with AERD. With montelukast pretreatment, classic upper and lower respiratory tract reactions are shifted to naso-ocular reactions,[34] and ambulatory procedures are often appropriate.[35] However, severe reactions can still occur during any desensitization procedure, and inpatient desensitization was modeled in sensitivity analyses to account for possible variation in practice. Even when more expensive inpatient conditions were considered, therapeutic desensitization remained a cost-effective approach for AERD. Repeat aspirin desensitization was not modeled; however, even for patients who require repeat procedures, the lifetime cost of ambulatory desensitization would be unlikely to exceed the costs of desensitization applied to the inpatient setting ($10,000 in current dollars). Because the use of alternative antiplatelet agents was marginally cost-effective in the base case, additional upfront costs of desensitization only attenuated the relative economic advantage of aspirin over clopidogrel. Also, we did not include additional benefits of aspirin desensitization with regard to the use of NSAID agents cross-reactive with aspirin for other associated medical conditions.[2,36,37] When considering comorbid conditions, such as osteoarthritis, the availability of aspirin and related agents in particular patients might lead to further cost savings and improvements in quality of life.

In our modeling of costs of asthma therapy, we did not consider the potentially considerable costs of omalizumab, which might be used in a subset of patients with AERD with concomitant IgE-mediated sensitivity to perennial allergens and severe asthma. If aspirin desensitization could reduce the need for omalizumab in such a patient subset, it would have even greater cost-effectiveness than our estimates.

Our analysis of aspirin desensitization used for secondary cardiovascular thromboembolic event prophylaxis did not include considerations of dual-antiplatelet therapy, which might be clinically indicated in some aspirin-sensitive patients. Dual therapy is used in the setting of antithrombotic therapy for intracoronary stent implantation. The majority of stents used today are drug-eluting stents, which are inherently thrombogenic. The risk of subacute in-stent thrombosis leading to death, myocardial infarction, or urgent target vessel revascularization has been greatly reduced by aggressive antithrombotic therapy.[38] In patients undergoing stent placement, the Seventh American College of Chest Physicians Conference on Antithrombotic and Thrombolytic Therapy applied a grade 1A recommendation to combination therapy with aspirin and a thienopyridine derivative, such as clopidogrel, over systemic anticoagulant therapy, and desensitization can be considered in such patients with an allergy to aspirin.[10,13,39] The Stent Anticoagulation Restenosis Study trial demonstrated a significant incremental benefit in terms of stent thrombosis when another antiplatelet agent was added to aspirin prophylaxis,[40] whereas the Clopidogrel in Unstable Angina to Prevent Recurrent Ischemic Events trial demonstrated similar protective effects in patients with acute coronary syndromes[41]; however, to our knowledge, evidence demonstrating such an incremental benefit when aspirin is added to clopidogrel is lacking. When aspirin was added to clopidogrel prophylaxis after recent ischemic stroke or transient ischemic attack in high-risk patients during the Management of Atherothrombosis with Clopidogrel in High-risk Patients trial, no significant incremental benefit was identified. Although no advantage of dual therapy was found in this population, patients in whom aspirin was added to clopidogrel experienced a greater rate of life-threatening bleeding, whereas no difference was reported in mortality.[42] Despite these uncertainties, dual therapy with antiplatelet agents is the established standard of care in some instances; however, our model was not designed to specifically investigate this question.

Aspirin desensitization is a cost-effective measure when used in patients with moderate-to-severe AERD. Although aspirin desensitization is the less-expensive alternative for patients with aspirin allergy requiring secondary cardiovascular prophylaxis, the use of clopidogrel is marginally cost-effective. From an economic standpoint, therapeutic aspirin desensitization should be strongly considered in patients with moderate-to-severe AERD. Although aspirin desensitization is cost saving, clopidogrel is also a reasonable option for patients with aspirin allergy requiring secondary cardiovascular prophylaxis, particularly in centers where aspirin desensitization is unavailable.

Clinical implications: From an economic standpoint, clopidogrel is a reasonable alternative for patients with AERD requiring secondary cardiovascular prophylaxis, and therapeutic aspirin desensitization should be strongly considered in patients with moderate-to-severe disease.

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