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Prevention of Severe Adverse Drug Reaction Outcomes – The Need for Clinical Decision Making Process for Identification of High Risk Patients in Large and Diverse Populations

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Abbreviations: ADRs: Adverse Drug Reactions; NSAID: Non-Steroidal Anti-Inflammatory Drugs; ACEI : Angiotensin Converting Enzyme Inhibitors; RB: Receptor Blocker; ER: Emergency Room

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Although severe adverse drug reactions (ADRs) are a major contributor to morbidity/ mortality rates/costs, up to 50% of these adverse events can be prevented. To date, efforts of ADR prevention have relied upon the identification of high risk patients via models used to predict the likelihood of ADR outcomes without being specific about outcome type or the development of clinical rules geared at a limited set of ADRs, predominantly bleeding outcomes.

Collectively, these efforts lack the methodology to address prevention in large and diverse populations. This short report showcases a process designed to identify the desired volume of patients at high risk of severe ADRs for large/diverse populations as a function of multiple criteria including traditional statistical metrics (e.g., sensitivity), economic (e.g., cost-savings) and best practices (e.g., % of desired prevention intervention improvement) with the dual goals to improve the quality and cost of care. The methodology is applied to major and non-major bleeding, and acute kidney injury outcomes for a wide spectrum of the US population representing the Commercial (working population and dependents) and Government programs (Medicare – individuals who are 65+ years; Medicaid – socially disadvantaged individuals with limited income). Practical challenges are discussed to further improve efforts designed to advance the science of ADR prevention.

Introduction

Pharmacologic treatments are an essential strategy in the care delivery journey for chronic patients worldwide. While they carry tremendous beneficial effects in care management interventions, medications may cause adverse drug events such as adverse drug reactions (ADRs) due to drug usage at normal doses [1-4]. The area of suspected severe ADRs (i.e., adverse outcomes occurring at any moment in time after post-drug marketing [2]) is of particular importance because, although they are a major cause of morbidity and mortality [5-9], about 45% of inpatient visits and 52% of outpatient visits induced by these ADRs can be prevented [10]. Consequently, the prevention of severe ADRs becomes a good value proposition and an important strategy to improve both the cost and quality of care for pharmacologic treatments.

To combat severe ADRs, two schools of thoughts emerged. First, the identification of patients at high risk for ADRs have relied on predictive models using the event likelihood as the outcome of interest [11-13]. In these efforts, severe ADRs have not been examined distinctively (e.g., major bleeding). This prompted some authors to express the need for explicit specification of ADR outcomes (e.g., major bleeding, acute kidney injury) so as to:

a) develop customized actionable interventions to prevent specific ADR outcomes

b) potentially improve the performance of developed predictive models [14]

The second set of efforts relied on the development of clinical rules designed for distinctive severe ADRs and primarily aimed at specialty care providers. These efforts have concentrated on

major (e.g., intracranial bleeding) and non-major bleeding (e.g., gastrointestinal bleeding) [15-21], with emphasis on the elderly population and in some instances these efforts were based on small sample sizes. In addition, limited attempts made use of predictive models to predict the risk of major and non-major bleeding in a national UK population [22]. Collectively, the efforts have emphasized the identification of high risk individuals without giving adequate guidance for the translation of research findings to practice for ADR prevention particularly for large and diverse populations.

The objective of this short report is to advance the science of ADR prevention by showcasing a process designed to identify patients at high risk of ADRs within the context of large and diverse US populations including Commercial (working population and dependents) and Government (Medicare – individuals who are 65+ years; Medicaid – socially disadvantaged individuals with limited income) lines of business in managed care organizations. The specific aims are

a. to assess severe ADR outcomes in terms of annual incidence rates and healthcare costs for diverse US populations and

b. to present a process designed to identify patients at high risk of ADRs in large and diverse US populations as a function of validation parameters for ADR predictive models, economic measures utilizing cost-savings calculations, and best practices in managed care organizations.

Methods

Program background

A program has been developed at Anthem Blue Cross and Blue Shield in order to monitor and prevent severe ADRs across a wide spectrum of the US populations exposed to different medications and spanning the Commercial, Medicare and Medicaid lines of business. Initially, the ADR monitoring and prevention program has been generated for eleven severe ADRs: major bleeding, non-major bleeding, acute kidney injury, hypotension, severe hypotension, acute liver injury, hyponatremia, uncontrolled hyperglycemia, hyperkalemia, and hypokalemia. This short report present examples of this work for major bleeding, non-major bleeding and acute kidney injury.

Outcome and exposure definition

The definitions of major bleeding, non-major bleeding, and acute kidney injury are provided in Table 1. Major and non-major bleeding may arise from exposure to anti-coagulants and anti-platelets. Anti-coagulants include warfarin and oral agents such as dagibatran, apixaban, betrixaban, edoxaban, and rivaroxaban. Furthermore, anti-platelets consist of aspirin, dipyridamole, abciximab, eptifibatide, tirofiban, cilostazol, vorapaxar, anagrelide, clopidogrel, prasagrel, ticlopidine, cangrelor, aspirin-dipyridamole. Acute kidney injury may be induced from individual or interactions of angiotensin converting enzyme inhibitors (ACEI) and receptor blocker (ARB) (e.g., benazepril, captopril, enalapril), diuretics (e.g., bumetanide, furosemide, torsemide), and non-steroidal anti-inflammatory drugs (NSAID) (e.g., diclofenac, etodofac, fenoprofen).

Calculation of incidence rates and healthcare costs

The target population for each of the aforementioned lines of business (Commercial, Medicare, Medicaid) were those exposed to the medications described above. All ADR outcomes were identified using ICD-10 codes documented in Table 1.

The medical databases were used as the data sources for the calculation of incidence rates and healthcare costs incurred during the 2016 fiscal year (Jan 1-Dec 31). An incidence was identified as the first event occurring in 2016 for a given individual. The incidence rate was calculated as the number of new events per 1000 of exposed population. The total healthcare expenditures associated with the ICD-10 in question for a given individual were computed for all emergency room (ER) and inpatient stay visits. Average costs are reported. All analyses were conducted using the Statistical Analysis Software [23].

Process for identification of patients at high risk of severe ADRs

The identification of patients at high risk of severe ADRs is a complex process requiring multiple criteria designed to reach this important clinical outcome in large and diverse segments of the population. The parameters and algorithm used the process are described in the following sections.

Validation parameters for predictive models. In this short report, we document the validation metrics for the ADR predictive models for major bleeding, non-major bleeding and acute kidney injury outcomes. These models were trained and tested as part of the tracking and prevention program of severe ADR outcomes as previously explained. The best models for acute kidney injury and non-major bleeding were obtained using the gradient boosting techniques (areas under the curve being 0.89 and 0.75, respectively for both models) and the random forest technique produced the best model for major bleeding (area under the curve=0.91). A technical comparison of random forest and gradient boosting techniques is provided elsewhere [24]. The input variables represent data derived from claims databases over a 24-month period and the outcome variables include ER and hospital admission events for the respective ADR defined in terms of ICD-10 codes over a 3-month period.

The validation metrics are described in terms of two sets of outcomes [25].

The first set of outcomes includes:

I. true positive (likelihood of a patient predicted by the model as high risk when he/she has the outcome of interest)

II. false positive (likelihood of a patient predicted by the model as high risk when he/she does not have the outcome of interest)

III. true negative (likelihood of a patient predicted by the

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model as low risk when he/she does not have the outcome of interest)

IV. false negative (likelihood of a patient predicted by the model as low risk when he/she has the outcome of interest).

The second set of outcomes consists of:

i. sensitivity (proportion of the population who experiences the outcome of interest that the prediction model successfully identifies)

ii. positive predicted value (proportion of patients who are identified by the model as high risk that will truly experience the outcome being predicted)

iii. specificity (proportion of the population who does not experience the outcome of interest that the prediction model successfully identifies)

iv. negative predicted value (proportion of patients who are identified by the model as low risk that will not truly experience the outcome being predicted)

v. accuracy (the proportion of patients who are predicted correctly by the model as high risk and low risk) for three ADR models (major bleeding, non-major bleeding, acute kidney injury).

Economic criteria and best practices. With the advancements of information technologies, provider messaging alerts are a potential strategy for actionable ADR prevention interventions delivered via customized information sent from managed care organizations and obtained from claims data processing at the patient level. These message alerts are usually prepared for high risk patients identified via predictive modeling. For each patient, a list of the most important risk factors is summarized together with a recommendation for drug therapy changes.

With the above in mind, a major question arises as to how to calculate the optimum volume of high risk patients identified by the predictive model in order to prevent severe ADR from cost effectiveness standpoint. Based on our experience, the volume of high risk patients depends on multiple criteria including the traditional statistical validation metrics described in the previous section, cost-savings calculations together with rules of thumb based on best practices. Similar to the validation metrics, the costs, savings, saving/cost ratios were computed for the top population percentiles (from 1 to 50%). That is, the population percentiles were rank ordered according to the probability of risk from higher to lower.

The costs included the expenditures attributed to the interventions designed for messaging the information to the providers including mailing and information technology infrastructure costs. The savings were calculated in terms of the improvement achieved in terms of emergency room and inpatient visit prevention for the ADR outcomes of interest (major bleeding, non-major bleeding, and acute kidney injury).

Different scenarios were generated for different costs (calculated per patient in the targeted volume for messaging to the providers) and effectiveness levels of ADR prevention (i.e., % of savings achieved in terms of emergency room and inpatient stay visits). A detailed discussion can be found elsewhere based on cost-savings calculations for medical events [26].

In addition to the above, a discussion of different stakeholders brought into light the need to incorporate best corporate practices typically implemented in clinical programs. One such a practice involves the incorporation of a cost-saving ratio of 3:1 to achieve satisfactory results. Another practice is the determination of a conservative estimate for the level of improvement required for prevention purposes. It was established that a 15% prevention improvement would be a good start for such efforts. In addition, a savings level of at least $200K per ADR outcome is required to offset indirect costs not typically included in the cost of interventions.

Algorithm integrating multiple criteria for clinical decision making process. The algorithm relies on optimizing the above mentioned multiple criteria by determining the minimum values for inclusion in the algorithmic process. As such, a decision is reached to distinguish high risk from low risk patients with the desired target volume for provider messaging.

Results

Incidence rates and healthcare costs for severe ADR outcomes

The incidence rates and healthcare expenditures for ER and inpatient stay visits are summarized for bleeding and acute kidney injury (Table 1). Bleeding has been identified as major (e.g., intracranial) and non-major (e.g., gastrointestinal) and is induced as adverse events of anticoagulants and antiplatelet agents. In general, major bleeding is a rarer event (1 for ER and 2.13 for hospital admissions per 1000 population) relative to non-major bleeding (15.69 for ER and 9.04 for hospital admissions per 1000 population) and is much costlier in terms of healthcare system consumption and usage ($56,133 for major bleeding inpatient stay relative to $ 13,393 for non-major bleeding).

Acute kidney injury is also a rarer event than non-major bleeding in terms of ER and inpatient stay incidence rates. On the other hand, the average cost for an inpatient stay is comparable for both ADR outcomes. While the incidence rates for acute kidney injury are higher than those for major bleeding, the average cost of inpatient stay is slightly less than 25% of that for major bleeding.

In general, the annual ER or inpatient incidence rates for the Medicare population are the highest followed by those for the Medicaid population, then the Commercial cohorts. On the other hand, the average healthcare expenditure per person in the Medicare population is the lowest, followed by the Medicaid,

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then the Commercial populations. It should be pointed out that the Medicare program has strict government contracting rules, thereby, explaining the lower medical costs despite the high incidence rates among all populations. The demographic characteristics of the populations exposed to medications are documented in Table 1.

Table 1: Severe ADRs – outcome and exposure definition, incidence rates and healthcare costs

Part a: ADR outcome and exposure definition

Severe ADR Outcome	Outcome Definition	ICD-10 Codes	Medication Exposure
1. Major Bleeding	Any bleeding event contributing to death, clinically overt bleeding associated with a fall in haemoglobin level of ≥ 2 g/dL or leading to transfusion of at least 2 units of packed RBCs, or bleeding with in a critical organ (including intracranial, retroperitoneal, intraocular, adrenal gland, spinal, or pericardial bleeding). For example, intracranial bleeding may include subarachnoid haemorrhage, intracerebral haemorrhage, subdural or extradural haemorrhage, and other unspecified intracranial bleeds.23	see Hippsley and Coupland21	Anticoagulants and antiplatelet agents21
2.Non-Major Bleeding	Overt gastrointestinal bleeding (except for insignificant hemorrhoidal bleeding), gross haematuria (macroscopic and lasting longer than 24h), substantial epistaxis that required intervention and was recurrent and/or lasted at least 5 min; extensive hematoma or bruising (5 cm in diameter), intraarticular bleeding (documented by aspiration), or menorrhagia or metrorrhagia (increased quantity or duration).23	see Hippsley and Coupland21	Anticoagulants and antiplatelet agents21
3. Acute Kidney Injury	An acute increase in serum creatinine and/or reduction in urine volume. It results in the abrupt loss of kidney function leading to the retention of waste products, electrolyte disturbances and volume status changes.24	N141 (Nephropathy induced by other drugs, medicaments, or biological substance), N170 (Acute kidney failure with acute cortical necrosis), N172 (Acute kidney failure with medullary necrosis), N178 (Other acute kidney failure), N179 (Acute kidney failure, unspecified), N19 (Unspecified kidney failure), N990 (Post procedural kidney failure), R34 (Anuria and oliguria), R944 (Abnormal results of kidney function results)	Angiotensin-converting enzyme inhibitors (ACEI), angiotensin-receptor blocker (ARB), diuretics, non-steroidal anti-inflammatory drugs (NSAID).25

Part b: ADR incidence rates and healthcare costs

Severe ADR Outcome	Type of population	Annual ER Incidence Rate (per 1000)	Cost/ER Visit ($)	Annual Inpatient Incidence Rate (per 1000)	Cost/Inpatient Stay ($)
1.Major Bleeding	Commercial	0.75	1509	1.49	92196
	Medicare	1.38	735	3.01	27340
	Medicaid	0.58	445	1.29	67340
	Overall	1	1072	2.13	60624
2.Non-major Bleeding	Commercial	11.1	916	5.17	18749
	Medicare	21.55	515	13.14	11354
	Medicaid	13.05	252	4.92	12624
	Overall	15.69	653	9.04	14464
3.Acute kidney Injury	Commercial	0.41	1148	1.53	21190
	Medicare	1.7	1296	5.64	9369
	Medicaid	1.13	373	3	9233
	Overall	1.13	1081	3.57	14202

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Part C: Demographic characteristics of population exposed to medications

				Age (Years)	
Exposure	**Line of Business**	**Gender**	**Count**	**Average**	**SD**
Anticoagulants/Antiplatelets	Commercial	Female	154467	56.5	12.5
		Male	279738	57.7	10.2
	Medicare	Female	97834	49.2	14.3
		Male	90862	51	13.1
	Medicaid	Female	57218	75.5	10.6
		Male	55806	73.3	10
	Total	Female	309519	61.2	15.9
		Male	426406	60.2	12.8
		All	735925	60.6	14.2
ACEI/ARB/Diuretics/NSAID	Commercial	Female	2177042	50	13.4
		Male	2060515	51.7	12.4
	Medicare	Female	715235	32.8	18.3
		Male	420891	30.6	21.4
	Medicaid	Female	447852	72.3	11.4
		Male	2,85,210	70.7	11.1
	Total	Female	3340129	49.3	18.3
		Male	2766616	50.5	17.3
		All	6106745	49.8	17.9

Process for patient identification at high risk of ADRs

Validation metrics for severe ADR predictive models. To prevent severe ADR outcomes in scaled up diverse populations, the question becomes what is the method used in determining the volume of targeted patients for prevention purposes. This question is answered with the information provided in this section and the following one. Traditionally, the first step in this process is to determine the probability thresholds corresponding to acceptable levels of sensitivity, specificity, and positive predictive value. The validation metric for the three ADR predictive models are provided in Table 2.

Table 2: Validation metrics for severe ADR prediction models

	Major Bleeding (AUC=0.91)					Non-major Bleeding (AUC=0.75)					AKI (AUC=0.89)				
perile	**Sen**	**Spec**	**PPV**	**NPV**	**Acc**	**Sen**	**Spec**	**PPV**	**NPV**	**Acc**	**Sen**	**Spec**	**PPV**	**NPV**	**Acc**
1	23.5	99	3.2	99	99	8.4	99.1	10.3	98.9	98	27.3	99.1	11.2	99.1	98.8
2	39.2	98	2.6	98	98	13.5	98.1	8.3	98.9	97.1	38.8	98.2	7.9	98.2	97.9
3	47.1	97.1	2.1	97.1	97.1	17.5	97.2	7.1	99	96.2	45.2	97.2	6.2	97.2	97
4	52.9	96.1	1.8	96.1	96.1	21.5	96.2	6.6	99	95.3	50.6	96.2	5.2	96.2	96
5	64.7	95.1	1.7	95.1	95.1	23.7	95.2	5.8	99	94.4	55	95.2	4.5	95.2	95
6	68.6	94.1	1.5	94.1	94.1	26.7	94.3	5.5	99	93.4	58.6	94.2	4	94.2	94.1
7	70.6	93.1	1.4	93.1	93.1	29	93.3	5.1	99.1	92.5	61.6	93.2	3.6	93.2	93.1
8	74.5	92.1	1.3	92.1	92.1	31	92.3	4.8	99.1	91.5	64.1	92.2	3.3	92.2	92.1
9	76.5	91.1	1.1	91.1	91.1	33.5	91.3	4.6	99.1	90.6	65.9	91.2	3	91.2	91.1
10	76.5	90.1	1	90.1	90.1	35.5	90.3	4.4	99.1	89.6	68.7	90.2	2.8	90.2	90.2
11	78.4	89.1	1	89.1	89.1	36.8	89.3	4.1	99.1	88.7	70.6	89.2	2.6	89.2	89.2
12	78.4	88.1	0.9	88.1	88.1	39.8	88.3	4.1	99.2	87.7	72.2	88.2	2.5	88.2	88.2
13	78.4	87.1	0.8	87.1	87.1	40.9	87.3	3.9	99.2	86.8	73.9	87.2	2.3	87.2	87.2
14	78.4	86.1	0.8	86.1	86.1	44.3	86.4	3.9	99.2	85.9	75.1	86.2	2.2	86.2	86.2
15	80.4	85.1	0.7	85.1	85.1	46	85.4	3.8	99.2	84.9	76.2	85.2	2.1	85.2	85.2
16	84.3	84.1	0.7	84.1	84.1	48.4	84.4	3.7	99.2	84	76.9	84.2	2	84.2	84.2
17	84.3	83.1	0.7	83.1	83.1	49.9	83.4	3.6	99.3	83	77.7	83.2	1.9	83.2	83.2
18	84.3	82.1	0.6	82.1	82.1	51.6	82.4	3.5	99.3	82	78.8	82.2	1.8	82.2	82.2

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19	84.3	81.1	0.6	81.1	81.1	54.4	81.4	3.5	99.3	81.1	79.5	81.2	1.7	81.2	81.2
20	84.3	80.1	0.6	80.1	80.1	55.5	80.4	3.4	99.3	80.1	80.1	80.2	1.6	80.2	80.2
21	84.3	79.1	0.5	79.1	79.1	57.4	79.5	3.4	99.3	79.2	81	79.2	1.6	79.2	79.3
22	86.3	78.1	0.5	78.1	78.1	58.3	78.5	3.3	99.3	78.2	81.6	78.2	1.5	78.2	78.3
23	88.2	77.1	0.5	77.1	77.1	59.8	77.5	3.2	99.4	77.2	82.7	77.2	1.5	77.2	77.3
24	88.2	76.1	0.5	76.1	76.1	60.9	76.5	3.1	99.4	76.3	83.9	76.2	1.4	76.2	76.3
25	88.2	75.1	0.5	75.1	75.1	61.3	75.5	3	99.4	75.3	84.9	75.2	1.4	75.2	75.3
26	90.2	74.1	0.5	74.1	74.1	62.2	74.4	2.9	99.4	74.3	85.3	74.2	1.3	74.2	74.3
27	90.2	73.1	0.4	73.1	73.1	63.7	73.5	2.9	99.4	73.3	86.1	73.2	1.3	73.2	73.3
28	90.2	72.1	0.4	72.1	72.1	64.5	72.5	2.8	99.4	72.4	87.1	72.2	1.3	72.2	72.3
29	90.2	71.1	0.4	71.1	71.1	64.7	71.4	2.7	99.4	71.4	87.5	71.2	1.2	71.2	71.3
30	90.2	70.1	0.4	70.1	70.1	66.2	70.5	2.7	99.4	70.4	87.9	70.2	1.2	70.2	70.3
31	92.2	69.1	0.4	69.1	69.1	68.4	69.5	2.7	99.4	69.5	88.2	69.2	1.2	69.2	69.3
32	92.2	68.1	0.4	68.1	68.1	69.7	68.5	2.7	99.5	68.5	88.7	68.2	1.1	68.2	68.3
33	92.2	67.1	0.4	67.1	67.1	70.5	67.5	2.6	99.5	67.5	89.3	67.2	1.1	67.2	67.3
34	92.2	66.1	0.4	66.1	66.1	71.8	66.5	2.6	99.5	66.5	89.8	66.2	1.1	66.2	66.3
35	92.2	65.1	0.4	65.1	65.1	72.3	65.5	2.5	99.5	65.5	90.1	65.2	1.1	65.2	65.3
36	92.2	64.1	0.3	64.1	64.1	73.3	64.5	2.5	99.5	64.6	90.6	64.2	1	64.2	64.3
37	92.2	63.1	0.3	63.1	63.1	73.5	63.5	2.4	99.5	63.6	91.2	63.2	1	63.2	63.3
38	92.2	62.1	0.3	62.1	62.1	74	62.4	2.4	99.5	62.6	91.7	62.2	1	62.2	62.3
39	92.2	61.1	0.3	61.1	61.1	74.8	61.4	2.4	99.5	61.6	92.5	61.2	1	61.2	61.3
40	92.2	60.1	0.3	60.1	60.1	75.9	60.4	2.3	99.5	60.6	92.9	60.2	0.9	60.2	60.4
41	92.2	59.1	0.3	59.1	59.1	76.3	59.4	2.3	99.5	59.6	93.3	59.2	0.9	59.2	59.4
42	92.2	58.1	0.3	58.1	58.1	76.6	58.4	2.2	99.5	58.7	93.7	58.2	0.9	58.2	58.4
43	94.1	57.1	0.3	57.1	57.1	77.2	57.4	2.2	99.5	57.7	94	57.2	0.9	57.2	57.4
44	94.1	56.1	0.3	56.1	56.1	78.1	56.4	2.2	99.5	56.7	94.3	56.2	0.9	56.2	56.4
45	94.1	55.1	0.3	55.1	55.1	79.1	55.4	2.2	99.5	55.7	94.6	55.2	0.9	55.2	55.4
46	94.1	54.1	0.3	54.1	54.1	79.8	54.4	2.1	99.5	54.7	95.1	54.2	0.8	54.2	54.4
47	94.1	53.1	0.3	53.1	53.1	80.2	53.4	2.1	99.5	53.7	95.6	53.2	0.8	53.2	53.4
48	94.1	52.1	0.3	52.1	52.1	80.6	52.4	2.1	99.5	52.8	95.8	52.2	0.8	52.2	52.4
49	94.1	51.1	0.3	51.1	51.1	81.1	51.4	2	99.5	51.8	96.1	51.2	0.8	51.2	51.4
50	94.1	50.1	0.3	50.1	50.1	82.4	50.4	2	99.6	50.8	96.5	50.2	0.8	50.2	50.4

Note: Perile – percentile; Sen – sensitivity; Spec – specificity; PPV – positive predicted value; NPV – negative predicted valu90.11e; Acc - accuracy

The results are shown for different top percentiles of the population (up to 50%). Furthermore, the threshold for detecting high risk patients as a function of sensitivity and specificity is reasonable (e.g., 65% or more for both measures). The positive predicted value (PPV), however, for the three severe ADR outcomes were in the low range with the highest values being around 3% for major bleeding, 10% for non-major bleeding, and 11% for acute kidney injury. Traditionally, the PPV values are in excess of 35% for valid models as measured in terms of area under the curve. The low values obtained for PPV are explained to a large part by the low incidence rates for severe ADRs, that is, rare medical events.

This in turn results in high false positives as shown in (Table 2). Therefore, this is a major issue which needs to be addressed for the proper prevention of severe ADRs. On the basis of the aforementioned results, one can conclude that traditional statistical measures of sensitivity, specificity and area under the curve cannot be solely relied on to make clinical decisions. Both true and false positives should also be taken into account for clinical decision-making for targeting volumes of high risk patients [27].

Economic criteria and best practices. The volume of targeted high risk patients usually depends in large part on cost-savings analyses as shown in Table 3. In this scenario, the cost per patient is estimated at $5.10 and the intervention is effective at preventing 15% of the ADR outcomes. Although cost-savings calculation is an essential ingredient in determining the optimum level of targeted high risk patients for prevention purposes, additional parameters should be taken into account. In essence, this process depends on multiple criteria including

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Table 3: Business cases

Part a: Cost-savings analyses

	Major Bleeding				Non-major Bleeding				Acute Kidney Injury			
Percentile	Cost	Savings	Net Savings	Savings/ Cost Ratio	Cost	Savings	Net Savings	Savings/ Cost Ratio	Cost	Savings	Net Savings	Savings/ Cost Ratio
1%	1933	64676	62676	33.5	1933	31947	30014	16.5	18355	615800	597445	33.5
2%	3866	107793	107793	27.9	3866	51606	47741	13.3	36710	875493	838783	23.8
3%	5799	129352	129352	22.3	5799	66351	60552	11.4	55065	1062099	1007034	19.3
4%	7732	145521	145521	18.8	7732	81915	74183	10.6	73420	1188058	1114639	16.2
5%	9659	177858	177858	18.4	9659	90107	80442	9.3	91775	1289136	1197362	14
6%	11592	188638	188638	16.3	11592	101575	89982	8.8	110124	1354449	1244324	12.3
7%	13525	194027	194027	14.3	13525	110585	97060	8.2	128479	1430646	1302167	11.1
8%	15458	204807	204807	13.2	15458	117958	102500	7.6	146834	1478853	1332018	10.1
9%	17391	210196	210196	12.1	17391	127787	110396	7.3	165189	1534834	1369645	9.3
10%	19319	210196	210196	10.9	19319	135160	115836	7	183544	1598591	1415048	8.7
11%	21252	215586	215586	10.1	21252	140075	118823	6.6	201894	1635913	1434019	8.1
12%	23185	215586	215586	9.3	23185	151543	128358	6.5	220249	1665459	1445210	7.6
13%	25118	215586	215586	8.6	25118	155639	130521	6.2	238604	1690339	1451736	7.1
14%	27050	215586	215586	8	27050	168745	141695	6.2	256958	1729216	1472257	6.7
15%	28978	220976	220976	7.6	28978	175298	146315	6	275313	1752541	1477228	6.4
16%	30911	231755	231755	7.5	30911	184309	153398	6	293663	1769647	1475984	6
17%	32844	231755	231755	7.1	32844	190043	157199	5.8	312018	1794528	1482510	5.8
18%	34777	231755	231755	6.7	34777	196596	161819	5.7	330373	1811633	1481260	5.5
19%	36710	231755	231755	6.3	36710	207245	170535	5.6	348728	1833404	1484676	5.3
20%	38638	231755	231755	6	38638	211341	172698	5.5	367083	1859840	1492757	5.1
21%	40571	231755	231755	5.7	40571	218713	178143	5.4	385438	1873835	1488398	4.9
22%	42503	237145	237145	5.6	42503	221990	179486	5.2	403787	1889386	1485598	4.7
23%	44436	242534	242534	5.5	44436	227724	183287	5.1	422142	1897161	1475019	4.5
24%	46364	242534	242534	5.2	46364	231819	185450	5	440497	1920487	1479990	4.4
25%	48297	242534	242534	5	48297	233458	185156	4.8	458852	1937592	1478740	4.2
26%	50230	247924	247924	4.9	50230	236734	186504	4.7	477207	1954698	1477491	4.1
27%	52163	247924	247924	4.8	52163	242468	190306	4.6	495557	1964028	1468471	4
28%	54096	247924	247924	4.6	54096	245745	191649	4.5	513912	1974914	1461002	3.8
29%	56024	247924	247924	4.4	56024	246564	190536	4.4	532267	1993574	1461308	3.7
30%	57956	253314	247924	4.3	57956	252298	194337	4.4	550622	2006015	1455393	3.6
31%	59889	253314	253314	4.2	59889	260490	200600	4.3	568976	2013790	1444813	3.5
32%	61822	253314	253314	4.1	61822	265405	203582	4.3	587326	2026230	1438904	3.4
33%	63755	253314	253314	4	63755	268681	204926	4.2	605681	2038671	1432989	3.4
34%	65683	253314	253314	3.9	65683	273596	207908	4.2	624036	2051111	1427075	3.3
35%	67616	253314	253314	3.7	67616	275234	207614	4.1	642391	2066661	1424271	3.2
36%	69549	253314	253314	3.6	69549	279330	209781	4	660746	2072882	1412136	3.1
37%	71482	253314	253314	3.5	71482	280149	208668	3.9	679096	2074437	1395341	3.1
38%	73415	253314	253314	3.5	73415	281788	208373	3.8	697451	2085322	1387872	3
39%	75342	253314	253314	3.4	75342	285064	209717	3.8	715805	2093097	1377292	2.9
40%	77275	253314	253314	3.3	77275	289160	211880	3.7	734160	2102428	1368267	2.9
41%	79208	253314	253314	3.2	79208	290798	211590	3.7	752515	2108648	1356133	2.8
42%	81141	253314	253314	3.1	81141	291617	210476	3.6	770870	2121088	1350218	2.8

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43%	83069	258703	258703	3.1	83069	294075	211001	3.5	789220	2124198	1334978	2.7
44%	85009	258703	258703	3	85009	297351	212345	3.5	807575	2133529	1325954	2.6
45%	86935	258703	258703	3	86935	301447	214508	3.5	825930	2136639	1310709	2.6
46%	88868	258703	258703	2.9	88868	303905	215037	3.4	844285	2139749	1295464	2.5
47%	90800	258703	258703	2.8	90800	305543	214743	3.4	862640	2142859	1280219	2.5
48%	92728	258703	258703	2.8	92728	307181	214448	3.3	880989	2147524	1266535	2.4
49%	94661	258703	258703	2.7	94661	308820	214153	3.3	899344	2153744	1254400	2.4
50%	96594	258703	258703	2.7	96594	313734	217135	3.2	917699	2158409	1240710	2.4

Table 3: Cont'd

Part b: Recommendations for volume of targeted patients

	Major Bleeding	Non-major Bleeding	AKI
Cost ($)	30911	57962	118029
Savings ($)	231755	252298	1445210
Savings/Cost Ratio	7.5	4.4	7.6
Probability Threshold (P^{ile})	16	30	12
Sensitivity (%)	84.30%	66.20%	72.20%
Specificity (%)	84.10%	70.50%	88.20%
PPV (%)	0.70%	2.70%	2.50%
NPV (%)	84.10%	99.40%	88.20%
Accuracy (%)	84.10%	70.40%	88.20%
Targeted Volume (TP+FP)	6061	11365	43186
Inflated Targeted Volume	7273	13638	51823

a. The levels of sensitivity, specificity and positive predictive values

b. Savings to cost ratio (e.g., 3 to 1 ratio)

c. Overall level of savings across all ADR outcomes (e.g., $200K).

Algorithm integrating multiple criteria. Table 3 provides a final summary of recommended volume of targeted patients which satisfies a number of criteria discussed among a number of stakeholders in the organization:

a) Reasonable sensitivity and specificity levels (e.g., > 65%)

b) Minimum levels of 3 to 1 savings/cost ratio

c) Overall savings in excess of $200,000 per ADR.

Due to the high rate of false positives, an inflation ratio of 20% was also implemented in order to safeguard against not achieving the best business practices particularly the amount of total savings per ADR outcome. It should be noted that the percentage of false positives is excessively high for severe ADR outcomes. This is a potential barrier which needs to be addressed in future research so as to improve the effectiveness of actionable interventions.

Discussion

Although severe ADR outcomes are life-threatening and have a major toll upon healthcare systems in terms of ER visits and hospital admissions, up to 50% of these ADR-related healthcare visits can be prevented. Therefore, it is paramount to address this issue as part of the larger issue of increased healthcare expenditures by advancing the science of ADR prevention. Traditionally, attention has been given only to identifying atrial fibrillation patients who are at high risk of bleeding via exposure to anticoagulants and antiplatelet agents [14-20]. These efforts have mostly relied on probability thresholds ingrained in statistical criteria or clinical scores to determine the high risk patients. In dealing with large and diverse volumes of patient populations, there is a need to develop a process which integrates scientific methods and criteria based on best business practices. The goal of this short report was to fill in this gap with the dual goals of improving the total cost and quality of care. Based on a review of the literature, it is very seldom that researchers report detailed model performance metrics (e.g., sensitivity, positive predicted value, accuracy, positive likelihood ratio, area under the curve) such as those documented in Piovella et al. [21].

This is necessary information to build cost-effective business cases for deploying actionable interventions in addition to the cost-savings criteria [26]. In the process, we have discovered that best business practices should be implemented in order to reach optimal clinical decisions for the ultimate prevention of severe ADRs such as the selection of cost-savings ratio, minimum savings required per ADR outcome, as well as, the % of prevention intervention a stakeholder is willing to adopt in order to determine the optimum volume of targeted patients in scaled-up and diverse populations.

One should note that severe ADR outcomes are rare medical events the prediction of which may yield a high percentage of

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false positive despite good valid metrics for the prediction model at hand. Potential solutions can be the development of clinical rules with customized information (e.g., detailed lab marker data) about the patient for post processing purposes in which the number of false positives is greatly reduced.

Other alternative would be the refinement of medication exposure profiles with an intent to increase the prevalence of ADR outcome in question [28]. Further research is warranted to address these barriers. Future efforts will report a clinical utility assessment of the provider messaging intervention destined to prevent severe ADRs. Collectively, there is a growing importance for the conduct of post-drug marketing studies to enrich the scientific literature about the adverse events and prevention of ADRs as advocated by regulatory agencies such as the US FDA [29-32].

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