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A Novel Approach to Estimating the Risk of Harm Due to Drug-Drug Interactions: An Exemplary Model with Common Mediations That Interact with Oral Anticoagulants

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Background

- Current drug-drug interaction (DDI) warnings lack details about the risk of harm and only evaluate 2 products
- DDI often assigned meaningless labels such as “Major” or “Contraindicated”
- Use of subjective terms concerning risk of harm is not useful to clinicians or patients
- Clinicians override more than 90% of DDI warnings, contributing to alert fatigue
- Novel approaches to represent risk of harm are needed

Objective

- To **model the risk of gastrointestinal bleeding** (GIB) for patients on oral anticoagulants (OAC) and:
- non-steroid anti-inflammatory (NSAIDs);
- antidepressants,
- accounting for other patient risk factors and medications

- Model is called: DDInteract

Methods

- A literature research was conducted in PubMed to identify risk of GIB based on age, previous history of GIB, OAC (warfarin, apixaban, rivaroxaban, dabigatran and edoxaban), NSAIDs, antidepressants, glucocorticoids, antiplatelets, aspirin and proton pump inhibitors (PPI)
- Bleeding risk was estimated by incorporating evidence across multiple studies using the following formula:

$$Y_i = \beta_0 + \beta_i X_i$$

Where X_i represents each risk factor and β_i represents exposure (0/1) for that risk factor.

- We estimated the likelihood of bleeding for hypothetical 100 using this formula: $Probability\ of\ GIB = \frac{e^{Yi}}{(1+eYi)}$.
- Predicted GIB rounded to nearest whole number

Results

The model was calibrated to estimate GIB risk of 2% for warfarin and 1% for apixaban. See Table 1.

OAC	GIB Risk	Attribute	GIB Risk
Warfarin	2.0	Age	2.5
Apixaban	1.2	Aspirin	1.6
Rivaroxaban	3.1	Antiplatelet	1.5
Dabigatran	3.0	Corticosteroids	1.8
Edoxaban	3.3	Hx of GI Bleed	6.7
SSRI		NSAID	
Bupropion	1.0	Celecoxib	1.0
Venlafaxine	1.1	Ibuprofen	1.8
Desvenlafaxine	1.1	Diclofenac	4.1
Fluvoxamine	1.1	Indomethacin	6.6
Mirtazapine	1.1	Naproxen	6.8
Escitalopram	1.2	Meloxicam	8.0
Paroxetine	1.2	Piroxicam	12.8
Duloxetine	1.3	Ketoprofen	13.6
Citalopram	1.3	Ketorolac	21.6
Fluoxetine	1.3	PPI	
Sertraline	1.4	Any PPI	0.7

Table 1. Model Inputs for Various Medications and Risk Factors

OAC oral anticoagulant; GIB gastrointestinal bleeding; SSRI serotonin selective reuptake inhibitors; NSAIDs: non-steroidal anti-inflammatory drugs; PPI: proton pump inhibitors;

Validation:

The model was examined for face validity using patient scenario to provide the estimation of the GIB according to his/her attributes and the drugs selected.

Figure 2A shows a 72 years old patient on apixaban and aspirin GIB risk
Figure 2B adding diclofenac
Figure 2C comparing GIB risk for diclofenac vs naproxen
Figure 2D comparing GIB risk for diclofenac plus PPI vs naproxen plus PPI
Figure 2E on diclofenac and comparing GIB risk for bupropion and sertraline
Figure 2F on diclofenac and omeprazole, comparing GIB risk for bupropion and sertraline

Figure 2A. DDInteract Risk Model: Displaying Estimated Risk of GIB for Simulated Patient

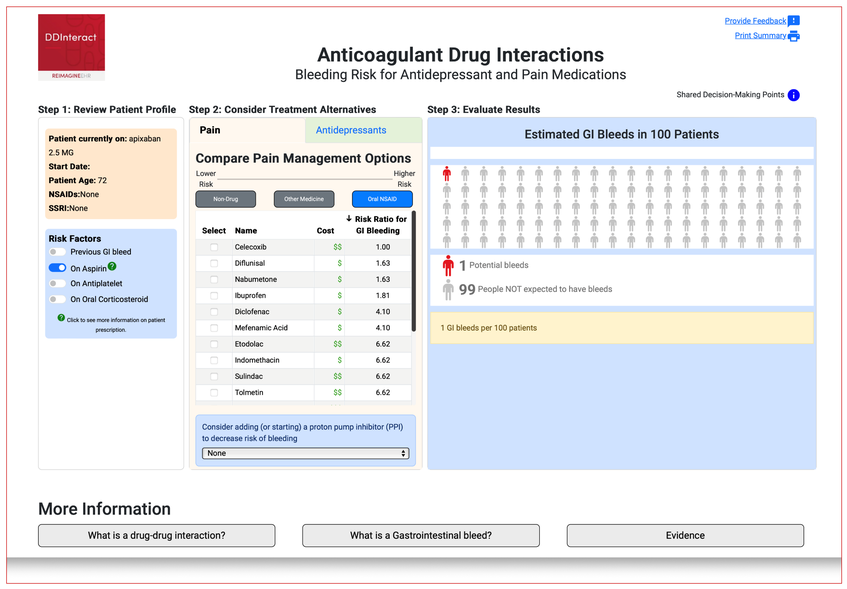


Figure 2B. Adding Diclofenac to Apixaban

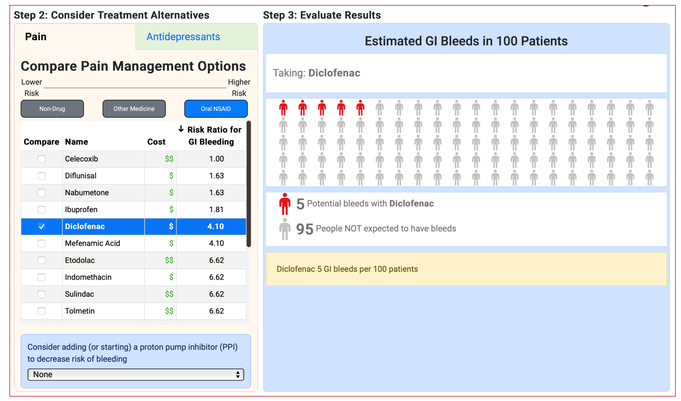


Figure 2C. Naproxen vs Diclofenac

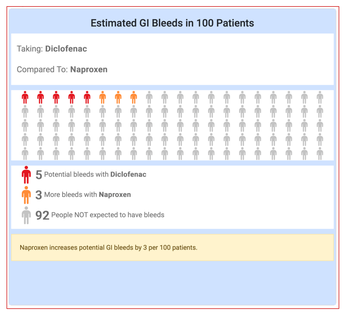


Figure 2D. Multiple Medications

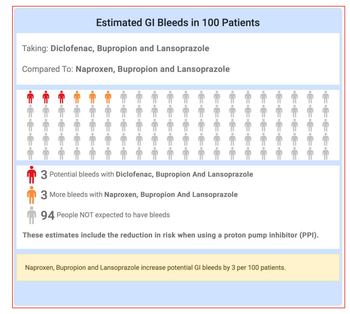


Figure 2E. Comparing Diclofenac and Bupropion / Sertraline

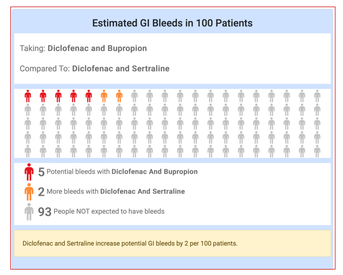
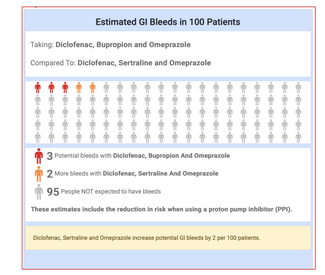


Figure 2F. Comparing Diclofenac/ Bupropion / Omeprazole



Conclusions

- The OAC GI bleeding risk calculator incorporates patient-level risk factors to estimate bleeding risk
- DDInteract allows clinicians to enhance share decision making when visiting patients on OAC that are receiving NSAIDs and/or antidepressants

References

DDI-CDS About us

DDInteract SMART app demonstration

For more information or a reprint of this poster, please contact Ainhoa G Lumbreras. email at **Ainhoa.Gomez-Lumbreras@pharm.utah.edu**