

# Thrombosis and Haemostasis 2023 Editors' Choice Papers

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This year's Editor's Choice highlights the 2023 publications in *Thrombosis and Haemostasis* (TH) and its open-access companion journal *TH Open*, focusing on manuscripts that have significantly resonated among our academic community. Unlike previous years since 2020, this year marks a notable shift, with coronavirus disease 2019 (COVID-19) papers no longer being in prime spotlight of TH publications. Instead, we have observed a trend toward integration of COVID-19 research within the broader context of cardiovascular studies.

## Working against the Clot

### Anticoagulation Management

The direct oral anticoagulants (DOACs) or nonvitamin K antagonist oral anticoagulants (NOACs) are becoming the gold standard, gradually replacing vitamin K antagonists and to some extent low molecular weight heparins. Beside the undeniable advantage of oral administration, they are also offering more predictable dosing, and reduced need for regular monitoring. Factor XIa (FXIa) inhibitors recently emerged as a yet newer class of anticoagulants, which directly targets FXI in the coagulation cascade. Galli et al<sup>1</sup> performed a useful pooled analysis gathering results from eight randomized controlled trials testing these new anticoagulants, suggesting that FXIa inhibitors had increased safety and efficacy in comparison to enoxaparin and even exhibited slightly enhanced safety compared with other oral anticoagulants.

When exploring new promising treatments, customizing existing anticoagulation strategies to align with patient's

need is crucial. We have published several studies last year, which investigated how age influences the management and efficacy of anticoagulation therapy. The Adage Study collaborators<sup>2</sup> collected real-life setting pharmacokinetic/pharmacodynamics data on the oral FXa inhibitors rivaroxaban and apixaban in aged atrial fibrillation (AF) patients. The high variability in drug levels observed should prompt improvement in DOAC dosing in this population. Tailored dosing strategy including information about genotype and the concomitant use of interacting drug(s), may reduce variability in drug levels, thereby improving clinical outcomes.<sup>3</sup>

The issue of polypharmacy, typically defined as the concomitant use of five or more medications, is indeed particularly relevant in elderly patients with AF, often associated with multiple health conditions, falls, frailty, and dementia. The study from Grymonprez et al<sup>4</sup> confirmed worse outcomes including increased bleeding and mortality risks associated with polypharmacy. NOACs demonstrated nonetheless superior benefit–risk profiles over vitamin K antagonists in AF patients with polypharmacy, in agreement with the pooled data meta-analysis on observational trials and post hoc subgroup analyses of randomized clinical trials from Zheng et al.<sup>5</sup> These findings stress the importance of managing polypharmacy in AF patients to enhance clinical care.

AF patients represent clinical complex patients,<sup>6</sup> and its management has evolved toward a holistic or integrated care approach, incorporating stroke prevention, rate or rhythm control, and cardiovascular risk factor and comorbidity management, including lifestyle factors.<sup>7</sup> Adhering to the recommended Atrial fibrillation Better Care pathway can

significantly impact AF outcomes, including mortality, stroke, and bleeding.<sup>8,9</sup> This approach is evident even in complex cases, and recommended in guidelines.<sup>10,11</sup>

Another issue is the clinical trial “underrepresentation” of elderly patients with comorbid conditions associated with a high bleeding risk. The study from Schenker et al<sup>12</sup> addressed this meaningful issue by investigating the large and well-known SWITCO65+ cohort of patients. They found that as much as one out of three patients could not have participated in a therapeutic trial evaluating oral anticoagulant in the treatment of acute venous thromboembolism (VTE), although this subpopulation has evolved a risk profile different from the eligible patients, and an increased risk of major bleeding. Such results should prompt clinicians to readdress VTE management in the elderly and more particularly trialists to review the design of future studies.

Cirrhotic patients receiving DOACs represent another group of patients for whom bleeding risk has not been systematically explored. Li et al<sup>13</sup> attempted to assemble the emerging evidence on this topic in an updated meta-analysis study and reassuringly suggested that bleeding associated with DOACs was not significantly elevated compared with other anticoagulants and might even be lower. With the advent of improved oral anticoagulants and enhanced management approaches, it may become possible to consider anticoagulation management in cases where it was not previously. However, it is equally imperative to evaluate its benefits and risks in these scenarios.

While residual vein thrombosis has no role in patient management according to actual international guidelines, a study by Iding et al<sup>14</sup> found that residual obstruction after deep vein thrombosis (DVT) indicated a higher risk of post-thrombotic syndrome which might prompt discussions on personalized care for VTE patients.<sup>15</sup> Interestingly, the authors also observed higher risk of arterial events, hinting at shared underlying mechanisms between venous fibrosis and atherosclerosis.

Another case where it is difficult to assess whether/how anticoagulation should be considered is after intracranial hemorrhage. The lack of robust evidence from large, randomized trials has led to uncertainty and thus, varying clinical practice on its use.<sup>16</sup> Schulman and colleagues<sup>17</sup> presented a retrospective series of intracranial hemorrhage cases developing VTE and suggested “stepwise escalation” of anticoagulation. Larger trials should offer clarity on this topic in the upcoming years.<sup>18</sup>

Regular monitoring of anticoagulant activity is crucial for ensuring successful management and safe administration of anticoagulation therapy. A French multicenter study<sup>19</sup> alerted to the significant overestimation of anti-Xa levels in anti-Xa assays using dextran-containing reagents post heparin neutralization by protamine, warranting caution. Adherence plays a pivotal role in the successful management of anticoagulants, significantly influencing effectiveness and treatment outcomes. Examining anticoagulation treatment patterns in South Korea, Yoon et al alerted us about country-specific obstacles to anticoagulant therapy. They investigated the uptake and persistence of anticoagulants in patients with

and without cancer-related VTE in China between 2013 and 2019.<sup>20</sup> Their findings underscored a significant gap in treatment continuation, notably in cancer-associated VTE cases, despite guidelines recommending indefinite anticoagulation, which was likely attributable to lack of drug reimbursement and drug affordability issues in China.<sup>21</sup>

### Antiplatelet Strategies

As with anticoagulants, antiplatelet therapy effectively decreases the risk of thrombosis but simultaneously elevates the risk of serious bleeding.<sup>22</sup> Dual-antiplatelet therapy (DAPT) intensifies this risk further, prompting studies to explore shorter DAPT durations, particularly in stable patients. Such bleeding risk is increased further among East Asians.<sup>23,24</sup> To address these issues, the systematic review and meta-analysis from Gorog et al<sup>25</sup> compared DAPT between East Asians and Western patients and highlighted that de-escalating DAPT in East Asians indeed reduced bleeding without sacrificing the anti-ischemic effect following acute coronary syndrome. The SWAP-AC Study<sup>26</sup> in turn offered significant evidence favoring the transition from DAPT to dual pathway inhibition in patients with coronary artery disease. Birocchi et al<sup>27</sup> performed three meta-analyses cumulatively including 21 trials with P2PY12-related therapy in patients undergoing percutaneous coronary intervention, which identified genotype and high on treatment platelet reactivity as guidance for antiplatelet treatment, most significantly in trials performed within China. This study should advance our understanding of personalized antiplatelet therapy, particularly for Asian regions characterized by elevated cytochrome P450 mutations.<sup>28</sup>

Amid the evolving landscape of COVID-19, exploring the potential of antiplatelet strategies stands as a promising avenue in addressing the thrombotic complications associated with this viral infection. Stefanini et al<sup>29</sup> reported higher sensitivity of platelets to ristocetin-induced agglutination in severe and short-term mortality COVID-19 patients compared with patients with mild symptoms, in line with previous observations on significant increase of von Willebrand factors (VWFs) circulating levels in COVID-19 patients and could be a useful tool to identify patients with high risk of clinical deterioration. Insights from the CORE-19 Registry revealed increased rates of arterial and VTE events, along with higher mortality in COVID-19 patients with prior cardiovascular risks, calling for exploration of the role of antithrombotic agents, particularly add-on antiplatelet therapy, through randomized controlled trials in the immediate postdischarge period.<sup>30</sup> In this respect, Rolling et al's highly cited paper<sup>31</sup> on the effect of antiplatelet therapy P2Y12 inhibition in COVID-19 was very welcome. Their findings align with previous studies in atherosclerosis patients, confirming monocyte platelet aggregate formation and its successful suppression through P2Y12 inhibition in COVID-19. Exploring other treatment choices for COVID-19 patients was also addressed by an extended follow-up of the (previously negative) INSPIRATION-S trial (atorvastatin vs. placebo), involving critically ill COVID-19 patients in the intensive care unit.<sup>32</sup>

### Intravenous Thrombolysis

In certain acute conditions, where anticoagulation or antiplatelet strategies might not suffice, actively dissolving blood clots becomes crucial, necessitating the use of thrombolysis while carefully assessing its risks. In a large multicentric retrospective observational study of acute ischemic stroke in China, Tu et al<sup>33</sup> addressed the debated efficacy of intravenous thrombolysis for minor stroke. Although associated with an increased probability of functional independence at 3 months, intravenous thrombolysis had no effect on mortality and appeared best reserved for people with disabling deficits, while DAPT may be better adapted to patients with nondisabling stroke syndromes.<sup>34</sup> In the context of DVT, catheter-directed thrombolysis is commonly used with insufficient consensus on ideal patient selection and considerable variation in protocols and outcome assessments. Duarte-Gamas et al<sup>35</sup> conducted a systematic review and meta-analysis to address this variability, which underscored the need for standardized reporting in catheter-directed thrombolysis protocols and patient-centered outcomes.<sup>36</sup>

### At Risk!

Having mentioned numerous studies addressing risks primarily linked to anticoagulant management, our scope now extends to additional pivotal risk factors implicated in both thrombosis and stroke. These encompass critical aspects, including gender disparities, the impact of obesity, previous thrombotic events, and the influence of various medical conditions like cancer. These factors have been under investigation of the Italian COPE study's report,<sup>37</sup> potentially the most extensive and contemporary on pulmonary embolism (PE) with over 5,000 patients from more than 180 sites and which should serve as a valuable data source on current disease patterns, management strategies, and outcomes of acute PE.

### Sex Differences

Female-specific biological factors, such as hormonal fluctuations during pregnancy, contraceptive use, and hormonal therapies, contribute to an increased risk of thrombosis and stroke. Understanding these distinctions is crucial for tailoring effective preventive measures and treatments in women's health care and we are glad that many studies last year reflected this important issue. The population level study from Hwang et al<sup>38</sup> on the occurrence of PE in pregnant women in Korea attracted particular attention. Although Asian women generally have a reduced risk of pregnancy-associated VTE, this risk is increasing, highlighting the importance for obstetricians to recognize VTE risks, particularly among patients displaying clinical high-risk characteristics.<sup>39</sup> Insights from the Italian multicenter START Registry<sup>40</sup> shed light not only on pregnancy but also oral contraceptives as a risk factor for VTE in women. The study underscored the importance of screening for a family history of VTE in women of childbearing age, particularly those pregnant or using contraceptives. Understanding these risk factors could aid in identifying at-risk women and guiding counseling, alternative contraceptive choices, or thromboprophylaxis during high-risk periods.<sup>41</sup>

The use of fertility drugs and hormones during assisted reproductive techniques is another risk factor for women for developing blood clots. The study from Goulou et al<sup>42</sup> emphasized how factors linked to infertility causes and drugs used in treatment contribute to this risk. While assisted reproductive techniques' efficacy is continuously enhanced, and becoming more common among older women with health issues, adequate research on minimizing potential health risks for women are urgently required.<sup>43</sup>

Corica et al discussed female sex as a risk factor for AF-related stroke, as women with AF still often receive less treatment with oral anticoagulants and suffer more severe AF-related strokes. Inclusion of female sex in the CHA<sub>2</sub>DS<sub>2</sub>-VASc score has led to increased oral anticoagulant management in women, countering the previous trend of lower anticoagulation usage among female AF patients.<sup>44</sup>

### Weight

Obesity is a yet commonly recognized risk factor for VTE and an increasing relevant issue that affects both initial VTE risk and recurrence risk. The Tromso Study group used a large, population-based cohort to explore the population-attributable fraction of VTE due to being overweight and obese<sup>45</sup> highlighting the importance of obesity in relation to VTE risk and adding to the available information on the population-attributable risk of obesity with VTE. Emerging research also explores the nuanced impact of body mass distribution on this condition, highlighting complexities beyond overall body weight. Wang et al<sup>46</sup> investigated the link between waist circumference and hip circumference with VTE, and particularly PE. They provided insights into visceral fat mass distribution as an independent risk factor for VTE. Importantly, the study from Gaugler et al<sup>47</sup> reassuringly confirmed that body mass index did not impact the effectiveness of age-adjusted D-dimer in patients suspected of having PE. While weight management may prove beneficial in reducing the burden of VTE,<sup>48</sup> preventing obesity in the first place should become a priority.<sup>49</sup> Certain type of dieting that venous thrombosis patients may be attempting are also associated with potential risks, as illustrated by the particularly intriguing case report, of an individual who developed DVT complication while on a zero-calorie diet regimen.<sup>50</sup>

### Medical Conditions

Conditions such as AF and cancer also are pivotal contributors to the heightened risk of thrombosis and stroke, often entwined with an increased susceptibility to bleeding complications due to anticoagulant therapy. As there is to date still no clear evidence on the clinical benefit of screening for AF, the exhaustive systematic review/meta-analysis protocol description from randomized trials from McIntyre et al<sup>51</sup> was very welcome in shedding light on an interesting and still not well-elucidated topic, namely, the impact of AF screening by electrocardiographic monitoring on stroke prevention.

The study from Ryu et al<sup>52</sup> suggested that thromboelastography could predict functional outcomes in acute ischemic stroke. They found a link between a hypercoagulable state (as identified by thromboelastography) and poorer

functional independence, symptomatic/asymptomatic hemorrhagic transformation, and early neurological decline. While thromboelastography shows promise in managing acute ischemic stroke, its definitive role in predicting outcomes requires further validation through large-scale randomized trials.<sup>53</sup> Romiti et al<sup>9</sup> showcased the significant advantages of Mobile Health Technology for Improved Screening and Optimized Integrated Care by a reanalysis of Atrial Fibrillation cluster randomized trial (mAFA-II trial), using the win ratio approach, a methodology that presents certain benefits compared with traditional analytical methods, particularly in trials evaluating composite endpoints.

Individuals diagnosed with cancer have a higher likelihood of experiencing VTE due to various factors, such as cancer-related inflammation and treatment methods. Assessing the risk factors, implementing preventive measures, and evaluating whether anticoagulant medications should be used are thus essential in cancer patients. In light of emerging anticancer drugs such as immune checkpoint inhibitor therapy, the challenges facing management of thrombotic and bleeding risks in cancer patients take a new dimension. le Sève et al's study<sup>54</sup> highlighted the high VTE rate in cancer patients, mostly with lung cancer or melanoma, undergoing immune checkpoint inhibitor therapy, primarily with nivolumab. This underscored the emerging challenge of VTE with immune checkpoint inhibitor therapy, prompting unanswered questions about its impact on survival, racial disparities, anticoagulant use, bleeding risks, and the mechanisms of thromboembolism during treatment, which require careful investigation, similar to previous generations of anticancer therapies.<sup>55</sup> In a prospective cohort with cancer-related VTE patients treated with anticoagulants, McBane et al<sup>56</sup> underscored the impact of recurrent VTE and bleeding on overall mortality, not just case fatality rate. Their data emphasized that anticoagulant-related bleeding is as crucial as recurrent VTE in predicting mortality among patients with cancer-associated VTE.<sup>57</sup> To address the specific need for predicting bleeding risk in patients with cancer-associated VTE undergoing anticoagulant therapy, Cohen et al<sup>58</sup> introduced the B-CT score, based on a thorough analysis of real-world data from over 15,000 patients with incident cancer-associated VTE patients treated with anticoagulants. The novel score identified various factors associated with increased bleeding risk in Ca-VTE patients, such as cancer type, history of bleeding, minor trauma, coagulation disorders, and specific comorbidities like stroke and gastrointestinal disease.<sup>59</sup> Rønnow et al examined the risk of cancer in patients with kidney disease after experiencing an initial VTE episode.<sup>60</sup> This study should alert physicians to be vigilant when focusing on kidney disease alone, as it could point to additional comorbidities and should reinforce existing guidelines recommending follow-up for patients 3 to 6 months postacute VTE potentially including cancer screening.<sup>61</sup> Other studies assessed safety of specific anticoagulation management in cancer patients. A retrospective review<sup>62</sup> indicated that both rivaroxaban and apixaban exhibited comparable effectiveness

and safety in treating cancer-associated thrombosis over a 6-month period, suggesting the most suitable anticoagulant should be considered with regard to patient preferences, adherence, and individual patient-specific factors.

Using data from the RIETE registry, Sigüenza et al<sup>63</sup> assessed the use of enoxaparin as a long-term treatment for VTE in cancer patients with renal insufficiency and observed that as renal function declined the likelihood of bleeding rose significantly, although the risk of recurrent VTE remained unchanged. A less, well-commonly studied risk factor for VTE is apnea, particularly obstructive sleep apnea, characterized by repeated episodes of upper airway obstruction during sleep. Intermittent hypoxia and inflammatory pathway activation could contribute to an increased risk of developing blood clots. Trzepizur et al<sup>64</sup> evaluated whether apnea markers were associated with unprovoked VTE incidence and found that the time spent under 90% of saturation could independently predict the risk of incident unprovoked VTE, but continuous positive airway pressure did unfortunately not play a beneficial role in VTE risk in sleeping apnea patients.

### (New) Techniques

We also welcomed new efforts into identifying or refining techniques to facilitate the identification of thrombosis risks. The study from the PE-EHR+ investigators<sup>65</sup> proposed to focus on the validity of electronic health records and administrative data analysis to identify acute PE patient cohorts. The PE-EHR+ study will be crucial to assess international classification of diseases codes and natural language processing methods for detecting acute PE hospitalizations. The meta-analysis from Squizzato et al<sup>66</sup> highlighted the high sensitivity and specificity of ventilation/perfusion single-photon emission computed tomography/computed tomography (V/Q SPECT/CT) lung scintigraphy techniques in detecting acute PE. Despite recommendations favoring CT pulmonary angiography as the gold standard offering greater anatomical detail, V/Q SPECT/CT might serve as a "low radiation" tool in follow-ups for selected acute PE survivors or other specific populations in stable conditions like pregnant women with suspected PE.<sup>67</sup>

### Getting to the Heart of the Matter

Following our presentation of the most influential clinical papers published last year, our focus now shifts to examining studies that investigated new mechanisms and targets in cardiovascular health. The diverse range of papers published in this field reflects the multifaceted nature and interconnected aspects of basic research published.

### New Biomarkers and Prognostic Tools

Pedersen et al<sup>68</sup> evaluated the potential of circulating micro-ribonucleic acids for prognostic purposes in a cohort of 900 stable patients with stable coronary artery disease and identified circulating miR-223-3p as predictor of stent thrombosis and major adverse cardiovascular event during follow-up, which may improve risk stratification in patients

with stable coronary artery disease. Using both clinical investigations and animal models, Liu et al<sup>69</sup> identified neutrophil extracellular traps (NETs) as a thrombosis risk marker and potential target for treatment in AF. However, it remains uncertain whether NETs play a causal role in initiating thrombosis or are merely associated with thrombotic events.<sup>70</sup> Risk of bleeding was sought by Lahu et al<sup>71</sup> who identified an association with soluble glycoprotein VI levels but no increased risk of ischemic events in patients undergoing elective percutaneous coronary intervention. This identifies soluble glycoprotein VI as a potential biomarker that warrants deeper investigation to assess its viability as a tool for personalized patient care.

### New Mechanisms

The debate on whether statins offer additional benefits beyond low-density lipoprotein (LDL) reduction was addressed by the study from Harm et al<sup>72</sup> who identified a distinct platelet lipid composition from statin-treated patients with symptomatic coronary artery disease, offering valuable understanding into the impact of statins that extends beyond mere LDL reduction. They discovered substantial changes in platelet membrane lipids, which might contribute to statins' additional effects. This study offers insights for future lipid studies, hinting at novel approaches to target lipids beyond simplistic increase or decrease strategies.<sup>73</sup> Chen et al<sup>74</sup> underscored the formation of neo-vessels within vasa vasorum in large arteries of type 2 diabetes patients, potentially contributing to atherosclerosis within the host vessel. Insights into neo-vessel formation in vasa vasorum could aid in identifying early vascular wall changes and determining suitable interventions to counter the development of atherosclerotic lesions.<sup>75</sup> High-fat diet encourages the formation of atherosclerotic plaques within the inner layer of arteries. Bianchini et al<sup>76</sup> investigated the impact of high-fat diet on bone marrow, using advanced imaging techniques and found that just 1 week of high-fat diet altered arteriole structures and hematopoiesis. Remarkably, these changes persisted even after 3 weeks on a normal diet, raising questions about its rapid influence of diet on hematopoiesis and long-term physiological alterations. The elevated numbers of neutrophils and monocytes also observed in the bone marrow pointed toward an alteration of the inflammatory response. The impact of another inflammatory mechanism, namely, tissue factor expression in monocytes and its induction by lipopolysaccharide in a spectrum of disease, was the topic of the comprehensive review by Sachetto and Mackman.<sup>77</sup> Encompassing sepsis and venous thrombosis, this study offers valuable insights into these pathological conditions. Platelet procoagulant physiology and its related abnormalities naturally continue to represent a dynamic focus of research published in TH. Recently, immature reticulated platelets gained attention for their potential prognostic role in cardiovascular diseases, especially coronary artery disease. A systematic review by Bongiovanni et al<sup>78</sup> found a link between higher reticulated platelets and increased risk of major adverse cardiovascular events in acute and chronic

coronary syndrome patients. While promising, using reticulated platelets as a routine prognostic tool requires further research to establish optimal parameters and cutoff values as well as to understand how different antiplatelet therapies affect patients with elevated reticulated platelets.<sup>79</sup> Kawano et al<sup>80</sup> developed a new mouse model using BxPC-3 cells to study pancreatic cancer's effect on altered platelet function and arterial thrombosis. They found reduced platelet counts but elevated reticulated platelets suggesting enhanced clearance of activated platelets. Gui et al<sup>81</sup> introduced a valuable PDE5A knockout mouse model which enabled them to identify PDE5A as a crucial enzyme for countering nitric oxide-induced platelet inhibition, leading to smaller clots and prolonged bleeding. The model should aid unraveling the complexities of cyclic nucleotide signaling pathways in platelets as well as evaluating therapeutic interventions targeting these pathways. The paper from Seidizadeh et al<sup>82</sup> investigated the mechanisms behind low VWF, a condition prevalent among many individuals who do, however, not all experience bleeding. The study revealed that diminished VWF synthesis/secretion and increased VWF clearance play contributing roles.<sup>83</sup> Importantly, Bourne et al<sup>84</sup> alerted to CLEC-2's distinct role in mouse and human platelets. While CLEC-2 is vital for thrombus growth in mice, it appeared to be less crucial for human platelet thrombus formation under arterial shear, raising key questions about CLEC-2's biological role in mice versus humans. Understanding species differences, as demonstrated in this study, is naturally crucial for identifying meaningful therapeutic targets with clinical use.<sup>85</sup> Other studies focused on specific mechanisms of the clotting process. Machado et al<sup>86</sup> highlighted the importance of manipulating factor FIX interactions with endothelial cells and connective tissue for clotting function. They demonstrated in two animal models that FIX mutants favoring extracellular binding improved hemostasis in comparison to other variants. Extravascular clotting activity of FIX and the underlying mechanism still need to be determined as well as clinical relevance.<sup>87</sup> In a thorough biochemical analysis, Souri et al<sup>88</sup> identified an anti-FXIII-B alloantibody, which developed in an FXIII-B-deficient patient after multiple plasma-derived FXIII concentrate treatments. This study questions the previous assumption that auto- and alloantibodies against FXIII-B lacked inhibitory effects and suggests instead that it might indirectly neutralize FXIII-B by impeding its binding to fibrinogen with important implications for successful treatment.<sup>89</sup>

As every year, we are pleased to have been able to share a range of scientific advancements and clinical observations, illustrating the various dimensions of TH. This past year has seen crucial investigations aimed at refining general clinical approaches to thrombosis, as well as at paving the way for new strategies in targeting biomarkers and understanding fundamental cardiovascular mechanisms. We are looking forward to the new and exciting discoveries and subsequent studies that the upcoming year will bring!

# Conflict of Interest

G.Y.H.L. is Consultant and speaker for BMS/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, Anthos. No fees are received personally. He is a National Institute for Health and Care Research (NIHR) Senior Investigator and co-principal investigator of the AFFIRMO project on multimorbidity in AF, which has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 899871.

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