Reduction in low-density lipoprotein cholesterol (LDL-C) decreases the burden of coronary artery disease. The 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) improve cardiovascular disease outcomes by reduction of LDL-C and are currently considered first-line therapy for patients with hypercholesterolemia. Recent evidence has resulted in current guidelines recommending a more aggressive approach, with lower LDL-C goals in high-risk patients. However, despite high doses of statin therapy, targets are not met in all patients. Ezetimibe reduces cholesterol levels, in particular LDL-C, by inhibiting the intestinal absorption of both biliary and dietary cholesterol. When combined with a statin, LDL-C levels are further decreased. Ezetimibe is therefore an attractive adjunct agent to statin therapy when LDL-C targets are not achieved, yet its clinical benefits on cardiovascular outcomes await additional clinical trials. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is an ongoing multicenter, randomized, double-blind trial that aims to determine whether the addition of ezetimibe to statin therapy improves cardiovascular outcomes in patients with acute coronary syndrome.

Keywords: ezetimibe • hypercholesterolemia • IMPROVE-IT • LDL
and stroke. A median LDL-C of 95 and 62 mg/dl was observed after 1 month in the standard and the intense therapy groups, respectively. At a mean follow-up of 24 months there was a significant 16% reduction in the hazard ratio in favor of the atorvastatin group for the primary end point (p = 0.005). Similar results were achieved in the Treating to New Target (TNT) trial [9] of patients with chronic stable CAD who were at lower absolute risk than the PROVE-IT patients. However, the Aggrastat to Zocor (A-to-Z) and Incremental Decrease in End Points Through Aggressive Lipid Lowering (IDEAL) studies [10,11], only demonstrated a nonsignificant trend towards the benefit of intensive statin therapy. Nonetheless, a subsequent meta-analysis of these four trials found that intensive statin therapy yielded a significant 16% odds reduction in coronary death or MI (p < 0.00001), as well as a significant 16% odds reduction in coronary death or any CV event (p < 0.00001) [12]. In view of these results the Adult Treatment Panel III (ATP III) of the National Cholesterol Education Program issued an update of their guidelines, acknowledging that a more aggressive goal of LDL-C of under 70 mg/dl in high risk CAD patients should be considered [13].

The need for combined therapy in hypercholesterolemia

Many high-risk CAD patients will achieve the strict LDL-C concentrations of less than 70 mg/dl; however, a significant proportion will not. The recently published Lipid Treatment Assessment Project 2 (L-TAP) survey from 15 European countries reported a 73% overall goal attainment; however, for the high-risk CAD patients, only 30% achieved LDL-C concentrations of under 70 mg/dl [14]. More aggressive treatment of patients not meeting targets and educating physicians about current guideline recommendations are likely to improve these figures. Nonetheless, doubling the doses of a statin only reduces cholesterol by approximately 6% [15]. Hence, it seems that despite appropriate dosage of statins and physician awareness of current guidelines, a significant proportion of patients will not reach their LDL-C targets. In addition, side effects of statin therapy, importantly rhabdomyolysis, although a rare event, are known to be dose dependent and can subsequently hinder the increase of statin dose in some patients [16]. Therefore, the addition of a second cholesterol-lowering agent seems to be an attractive option when LDL-C goals are not achieved by statin monotherapy.

Ezetimibe

Ezetimibe is the first of a new class of agents that inhibits intestinal absorption of cholesterol [17]. By mechanisms not completely understood, this is mainly achieved by blocking a protein transporter called Niemann–Pick CI-like 1 protein (NPC1L1), which is found at the apical membrane of the small intestine [18]. Through inhibition of NPC1L1 in the small intestine, absorption of dietary and biliary cholesterol and subsequent delivery of LDL-C to the liver is reduced [19]. Statins lower cholesterol by upregulation of hepatic LDL receptors, hence the combination of ezetimibe and statins results in both the inhibition of cholesterol intestinal absorption and the synthesis of cholesterol. Trials have shown that ezetimibe (10 mg) monotherapy significantly reduces LDL-C levels in hypercholesterolemic patients by -17.2 to -22.3% (p < 0.01 to < 0.001) when compared with placebo. When combined with a statin, ezetimibe significantly reduces LDL-C levels beyond those achieved by statin monotherapy. Interestingly, in add-on therapy studies ezetimibe is more effective in reducing LDL-C levels (-21.3 to -27%; p < 0.001) than when compared with combination studies (-5.9 to -21.0%; p < 0.05 to < 0.001) [20]. Genetic predisposition producing a different response to the two lipid-lowering drugs is likely to exist, since statins and ezetimibe exert distinct mechanisms of action. The improved response to ezetimibe observed in add-on studies could therefore, in part, be explained by a patient-selection bias. This is because those who respond poorly to a statin are more likely to be eligible for add-on ezetimibe treatment and at the same time are more likely to respond better to the aforementioned drug. Of note, current clinical practice is to use ezetimibe as add-on therapy; hence, results from similarly designed trials are probably more relevant. In addition, ezetimibe monotherapy significantly reduces triglyceride and ApoB-lipoprotein levels and increases high-density lipoprotein cholesterol levels when compared with placebo. These beneficial effects on the lipid profile are further improved when ezetimibe is coadministered with a statin [20]. Nevertheless, although ezetimibe monotherapy or in combination with a statin seems to positively alter the lipid profile, one should be aware of the relatively limited data available for this new drug when compared with the extensive existing body of evidence in favor of statin therapy.

From a safety perspective, ezetimibe is well tolerated when used as monotherapy or in combination with a statin [21]. Nonetheless, recent reports have caused concerns regarding a possible link between ezetimibe and increased risk of cancer [22]. However, a meta-analysis of three large ezetimibe trials did not find evidence to support this association [23].

Possible additional benefits of ezetimibe

Inflammation is nowadays considered an essential component in the development of atherogenesis and plaque rupture [24]. Elevated levels of high-sensitivity
C-reactive protein (hs-CRP), a marker of systemic inflammation, are linked with increased risk of ACS and ischemic stroke in asymptomatic patients [25]. It is therefore mentioned as an emerging clinical marker for the diagnosis and management of CAD in the ATP III guidelines [26] and in a scientific statement from the American Heart Association and CDC [27]. A recent study, Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) [28], showed that rosuvastatin significantly reduced the incidence of major CV events in healthy individuals without hypercholesterolemia but with elevated hs-CRP.

The evaluation of ezetimibe therapy and its effect on inflammation has generated, on the whole, positive results. A number of studies have shown that ezetimibe alone produces an overall modest, nonsignificant reduction in hs-CRP levels when compared with placebo [29]. However, when ezetimibe is combined with a statin, several studies support a synergistic effect on hs-CRP levels. For example, Pearson et al. reported a significant reduction in hs-CRP levels in patients receiving ezetimibe–simvastatin combination when compared with simvastatin alone in a pooled analysis of three trials, including 2541 patients (−31 vs −14.3%; p < 0.001) [30]. In addition, in a study by Ballantyne et al. comparing atorvastatin–ezetimibe combination therapy with atorvastatin alone, an overall larger reduction in hs-CRP levels was observed in the combination therapy group (−41 vs −31%; p < 0.01) [31]. By contrast, in a trial evaluating ezetimibe–simvastatin combination therapy compared with atorvastatin monotherapy no further reduction in hs-CRP was observed in the combined therapy group [21].

The mechanisms of this effect and the interaction with statins are not clearly understood. Moreover, there is conflicting evidence as to whether the anti-inflammatory effects of lipid-lowering therapies are largely secondary to their effects on LDL-C levels [30,32,33].

Lipid peroxidation is another novel risk factor for cardiovascular disease (CVD). Oxidized LDL is less likely to be taken up by hepatic LDL receptors and more prone to be taken up by monocytes in the arterial wall, which ultimately leads to endothelial injury and dysfunction. Hence, the oxidation of LDL is considered an early step in the process of atherosclerosis [34]. Statins are known to have a positive effect on LDL oxidation [35]. Ezetimibe has also been shown to reduce the serum level of oxidized LDL in a study [36] of 22 patients with hyperlipidemia and in a report of seven healthy subjects fed an oxidized cholesterol diet [37]. Nevertheless, the clinical implications for the positive effects on LDL oxidation are not known.

The ENHANCE & the ARBITER 6-HALTS controversy

Observational studies have shown that carotid artery intima-media thickness (CIMT) is associated with the risk of CVD [38]. It has therefore been used in many clinical studies as a surrogate end point of CVD. In the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study [39], changes in CIMT, measured by ultrasonography, were evaluated over 2 years of follow-up in 720 patients with familial hypercholesterolemia who were randomized to receive simvastatin 80 mg and either ezetimibe 10 mg or placebo. As expected, the combined therapy was more effective in reducing LDL-C (−39.1% vs 55.6%; p < 0.01) and hs-CRP (−49.2% vs −23.5%; p < 0.01) levels than simvastatin alone. However, despite this difference, the combined therapy did not result in a significant difference in changes in CIMT (p = 0.29). The Arterial Biology for the Investigation of the Treatment Effects of Reducing Cholesterol 6-HDL and LDL Treatment Strategies in Atherosclerosis (ARBITER 6-HALTS) trial [40] also evaluated changes in CIMT in patients taking ezetimibe. The study randomized 363 individuals with CAD or CAD equivalent, already on statin treatment, with LDL-C under 100 mg/dl and high-density lipoprotein cholesterol (HDL-C) under 50 mg/dl for men or less than 55 mg/dl for women to receive ezetimibe 10 mg or niacin 2000 mg. The primary end point was change in mean CIMT, measured by ultrasonography, after 14 months. The mean CIMT at baseline was 0.8978 ± 0.1516 mm. According to a prespecified interim analysis the study was terminated prematurely after 208 patients had completed the trial on the basis that niacin significantly reduced mean CIMT at 14 months (−0.0142 ± 0.0041 mm; p = 0.001) whereas ezetimibe did not affect mean CIMT when compared with baseline. There was a trend towards increased adverse CV events in the ezetimibe group compared with the niacin group, although this was not a primary end point (9 of 165 patients [5%] vs 2 of 160 patients [1%]; p = 0.05). Niacin significantly increased HDL-C levels by 18.4% and ezetimibe reduced LDL-C levels by 19.2%.

As one would imagine, the publication of these unfavorable results for ezetimibe has generated an intense debate, on the one hand questioning the clinical effectiveness of ezetimibe and on the other hand questioning the use of CIMT as a surrogate marker for CAD and the study design of both trials [41,42]. In ENHANCE the baseline CIMT in both groups was within the normal range (0.70 mm) and the majority of the study participants (81%) was already receiving statin therapy before...
entering the study. The latter could have allowed for CIMT stabilization and/or regression even before the study began and in that way dampening the potential effect of ezetimibe on CIMT changes throughout the study [43]. The mean baseline LDL-C in the ARBITER 6-HALTS trial was relatively low (84 mg/dl) and it is possible that ezetimibe does not affect CIMT at such low levels. Furthermore, the premature termination of the ARBITER 6-HALTS study, as recommended by an independent data advisory committee, resulted in CIMT not being measured at 14 months in more than 40% of the patients. Nonetheless, a recently published analysis by the same authors [44], adding 107 subjects who completed a close-out assessment (7 ± 3 months), provided evidence that strengthened their previously reported results. Still, it leaves some wondering whether ezetimibe could have had a positive effect on CIMT if the ARBITER 6-HALTS trial had been fully completed.

As a side note, the positive effects of niacin therapy on carotid artery atherosclerosis, as reported in the ARBITER 6-HALTS study, was confirmed in a study by Lee et al., who reported a significant reduction in carotid wall area in patients receiving a niacin–statin combination when compared with statin monotherapy [45]. By contrast, preliminary results from the National Institute of Aging (NIA) Plaque study reported no difference in the reduction of the volume of carotid atherosclerosis in patients treated with statin therapy combined with niacin or placebo [46]. The differences in the results can, in part, be explained by dissimilar HDL-C lipid levels. Patients from the NIA Plaque study had a higher HDL-C baseline level (55 mg/dl) than those from the ARBITER 6-HALTS (42 mg/dl) and the study by Lee et al. (38 mg/dl) which suggests that niacin is less effective at reducing carotid artery atherosclerosis at higher HDL-C levels.

Finally, although observational studies have shown that CIMT is an appropriate surrogate marker for CAD, a certain degree of overlap between the two pathologies is likely to exist. This is supported by a recent meta-regression analysis that reported a significant association between mean changes in CIMT and nonfatal MI [47], however, this relationship was not consistent in trials evaluating statin therapy or those with high baseline CIMTs. One should therefore be careful when linking reduced progression or reduction in CIMT with decreased CV events.

**IMPROVE-IT**

**Design & rationale**

To date, little is known about the clinical benefits of ezetimibe beyond the reduction of LDL-C. The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study evaluated the possible effects of ezetimibe combined with simvastatin on aortic valve stenosis when compared with placebo [22]. The study showed a significant reduction in ischemic events, which were defined as secondary end points (15.7 vs 20.1%; p = 0.02). However, the study was not primarily designed to evaluate the CV benefits of ezetimibe and the reduction in the ischemic events could have been due to the effect of simvastatin alone and not ezetimibe. The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) study is an ongoing randomized, double-blind, multicenter clinical trial that aims to evaluate whether the combination of ezetimibe and simvastatin will improve CV outcomes in high-risk patients, when compared with simvastatin alone [48,49]. The study has recently reached the enrollment goal of 18,000 patients [101].

The IMPROVE-IT study enrolled men and women diagnosed with ST-segment elevation myocardial infarction (STEMI) or non-STEMI (NSTEMI) or unstable angina (UA) within the last 10 days. The patients were selected on the basis of lipid criteria and presence of high-risk features. At 24 h of hospital admission, for patients who were not receiving a chronic lipid-lowering therapy, LDL-C levels had to be 50–125 mg/dl and 50–100 mg/dl for those who were receiving chronic statin therapy. Patients with STEMI had to have either an anterior MI or be at least 50 years old with evidence of elevated CV biomarkers, such as troponin and/or CK-MB and ECG findings consistent with new MI and UA/NSTEMI patients had to present ischemic discomfort at rest lasting at least 10 min and had to be at least 50 years of age and have at least one of the following findings: new ST-segment deviation of at least 1 mV, troponin or CK-MB elevation, diabetes mellitus, past history of previous MI, peripheral arterial disease or cerebrovascular disease, coronary artery bypass grafting (CABG) in the last 3 years, or known coronary multivessel disease including at least two major coronary arteries with stenosis more than 50%. The main exclusion criteria were failure of stabilization within the 24 h before enrollment due to the presence of hemodynamic, ischemic or arrhythmic events or when CABG was planned as the treatment of the ischemic event.

Approximately 1200 sites worldwide recruited participants who were randomized to receive, in a 1:1 ratio, either ezetimibe:simvastatin 10:40 mg or simvastatin 40 mg once daily. Based on results previously mentioned [20], the trial has predicted a steady-state difference of 15 mg/dl of LDL-C between the two study population. Furthermore, subjects in either arm, with LDL-C levels more than 79 mg/dl on two consecutive follow-ups have their simvastatin dose increased to 80 mg (Figure 1).

The primary end point is the time from randomization to the first episode of one of the following CV events: CV death, major coronary events (nonfatal MI, documented
UA requiring hospital admission, all coronary revascularization with either percutaneous coronary intervention or CABG occurring at least 30 days after randomization), or nonfatal stroke. Secondary end points include time from randomization to the first occurrence of death due to any cause, major coronary event or nonfatal stroke; CAD death, nonfatal MI or urgent coronary revascularization with either percutaneous coronary intervention or CABG occurring at least 30 days after randomization; CV death, nonfatal MI, documented unstable angina requiring hospital admission, all revascularization (including noncoronary) occurring at least 30 days after randomization, and nonfatal stroke. Tertiary end points will will evaluate the percentage of patients who achieve a ‘dual goal’ of LDL-C under 70 mg/dl and CRP under 2.0 mg/l and in addition correlate this to the clinical outcomes. Additionally, tertiary end points will include the evaluation of a variety of individual outcome measures. The study aims to continue until each participant has reached 2.5 years of follow-up and the target number of events (5250) is attained.

Current status

The IMPROVE-IT study recruited its first patient in October 2005 and the enrollment was as of June 2010 completed, resulting in a total number of 18,141 patients [49]. Baseline characteristics of the first 10,000 patients can be found in Table 1. In May this year, an update on the IMPROVE-IT design [49] was published in order to respond to the negative publicity regarding ezetimibe [50] that emerged following the ENHANCE trial and also to calm concerns about the trial’s length. The update states that a significant number of sites have been added in order to boost the enrollment and that the trial is expected to be completed in June 2013. Moreover, a second interim efficacy analysis will be carried out when 75% of the events had occurred (in addition to the original interim efficacy analysis at 50% of events). The IMPROVE-IT group argued that the probability of stopping the trial would be substantially higher with the additional interim analysis, with the impact on statistical power being relatively small.

Potential clinical implications

The IMPROVE-IT trial is the first definitive study to evaluate the effect of ezetimibe on CV outcomes. If a significant reduction in CV events in the ezetimibe–simvastatin arm compared with the simvastatin-only arm is found, it is likely that this will broaden the possible indications for ezetimibe therapy in hypercholesterolemic patients. First, it would be reasonable to consider the initiation of a combination of ezetimibe and a statin in patients with similar characteristics to those included in the IMPROVE-IT trial, namely high-risk patient with recent MI. Second, if the magnitude of the reduction in CV events is similar to that predicted by the regression estimate for statin effects, ezetimibe is likely to be beneficial as an adjunct to statin therapy in patients with higher LDL-C levels than those included in this trial who are otherwise unable to achieve desired LDL-C goals because of intolerance or incomplete efficacy of statin therapy. Third, the IMPROVE-IT trial will also evaluate the safety of ezetimibe, including cancer evaluation, and since it will accrue more than 80,000 patient-years, significant evidence on the safety of ezetimibe will emerge at the end of the trial.

In addition, if the reduction in CV events exceeds the expected regression line, non-LDL-mediated mechanisms are likely to play a part in the overall effect that ezetimibe has on clinical outcomes. If this is linked to reduced CRP levels it would suggest that a reduction of CRP levels cannot solely be attributed to reduced LDL-C levels. Also, the study will help to evaluate whether the LDL-C targets should be reduced further and may therefore have an impact on future clinical guidelines on lipid management.

By contrast, if the IMPROVE-IT study reports that combined ezetimibe–statin therapy produces no clinical benefits when compared with simvastatin monotherapy, with the previous negative results from the
in mind, the clinical effectiveness of ezetimibe will undoubtedly be further questioned. If, despite negative results, the LDL-C levels in the ezetimibe–simvastatin arms are found to be significantly lower than the simvastatin monotherapy arm, the explanation could be any of the following: lowering of LDL-C with ezetimibe is less effective in improving clinical outcomes than when a statin is used, probably due to statin nonlipid-mediated mechanism; or there might be a point at which further reduction of LDL-C does not translate into statistically significant clinical benefits. Indeed, the first 10,000 patients enrolled in the IMPROVE-IT trial had a relatively low LDL-C baseline (97 mg/dl) and therefore, a smaller clinical benefit is likely to be observed than if subjects with higher LDL-C levels had been included (Table 1). Nevertheless, with the study protocol of the IMPROVE-IT trial it would have been difficult to achieve LDL-C goals for patients with higher LDL-C levels, which would have been ethically unacceptable.

Conclusions
Ezetimibe is a novel cholesterol-lowering drug that reduces LDL-C levels by the inhibition of intestinal cholesterol absorption. This reduction is further improved when ezetimibe is coadministered with a statin. To date, the clinical impact of ezetimibe on CVD is not known; however, the ongoing IMPROVE-IT trial will help us answer this question. Negative results from the ENHANCE and the ARBITER 6-HALTS trials have led to the benefits and risks of ezetimibe being heavily debated. Subsequently, with these new issues in mind, we believe that the completion of IMPROVE-IT is vital. Furthermore, it is important to emphasize that the study aims to detect benefits from reducing LDL-C levels from low to very low, hence it is likely that the reduction in clinical events will be modest. Nevertheless, if the trial confirms that ezetimibe is safe and reduces CV outcomes, extension of its clinical indications is to be expected.

Future perspective
If the IMPROVE-IT trial demonstrates positive results in favor of the ezetimibe–simvastatin group, it is likely that combined therapy with ezetimibe for the management of hypercholesterolemic patients will be more frequently employed, especially in patients who fail to reach LDL-C targets with statin monotherapy. On the other hand, negative results would add fuel to the ongoing criticism about the clinical effectiveness of ezetimibe and undoubtedly question its role as a lipid-lowering agent in clinical practice.

Financial & competing interests disclosure
Luis Rodríguez-Padial has received research grants and honorariums from Merck Sharpe & Dohme, Lacer, Novartis and Servier and does consultancy for Merck Sharpe & Dohme and Servier. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

No writing assistance was utilized in the production of this manuscript.

Table 1. Baseline patient characteristics for the first 10,000 patients enrolled in the IMPROVE-IT trial.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (median, interquartile range; years)</td>
<td>62 (55, 70)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>77</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>22</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>17</td>
</tr>
<tr>
<td>Pre-enrollment coronary angiography</td>
<td>91</td>
</tr>
<tr>
<td>Pre-enrollment PCI after ACS event</td>
<td>76</td>
</tr>
<tr>
<td>Baseline LDL-C (median, interquartile range; mg/dl)</td>
<td>97 (81, 112)</td>
</tr>
<tr>
<td>– No prior lipid-lowering therapy</td>
<td>104 (89, 116)</td>
</tr>
<tr>
<td>– Prior lipid-lowering therapy</td>
<td>80 (68, 90)</td>
</tr>
<tr>
<td>Acute event</td>
<td></td>
</tr>
<tr>
<td>STEMI (%)</td>
<td>47</td>
</tr>
<tr>
<td>NSTEMI (%)</td>
<td>37</td>
</tr>
<tr>
<td>UA (%)</td>
<td>16</td>
</tr>
</tbody>
</table>

ACS: Acute coronary syndrome; LDL-C: Low-density lipoprotein cholesterol; MI: Myocardial infarction; NSTEMI: Non-ST-segment elevation myocardial infarction; PCI: Percutaneous coronary intervention; STEMI: ST-segment elevation myocardial infarction; UA: Unstable angina.

Reproduced with permission from [48].
The IMPROVE-IT trial: current status & potential clinical implications of ezetimibe

**Executive summary**

- The introduction of statins has greatly improved the treatment of hypercholesterolemia, thereby reducing the burden of cardiovascular (CV) disease.
- Recent evidence supports aggressive lowering of low-density lipoprotein cholesterol (LDL-C) concentrations below 70 mg/dl in high-risk patients. This is not always possible with statin monotherapy.
- Ezetimibe, which inhibits the intestinal absorption of cholesterol, effectively reduces LDL-C levels both when used as monotherapy and in association with a statin. It therefore constitutes an attractive adjunct agent to statin therapy when LDL-C targets are not met, yet its clinical impact on CV disease has not been studied.
- The Improved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is an ongoing randomized, double-blind, multicenter trial that enrolled approximately 18,900 patients. The trial is designed to assess whether the combination of ezetimibe and simvastatin will improve CV outcomes in patients with acute coronary syndrome. The primary end point is the time from randomization to the first episode of one of the following CV events: CV death, major coronary events, all coronary revascularization or nonfatal stroke. The trial is expected to reach completion in June 2013.
- Limitations in the study design of the IMPROVE-IT trial include a low LDL-C at baseline (97 mg/dl), observed in the first 10,000 patients enrolled. This could lead to a smaller clinical benefit, which is more difficult to statistically detect, compared with if patients with higher LDL-C had been included.
- If the IMPROVE-IT trial reports ezetimibe therapy to be safe and reduce CV outcomes, its future clinical indications are likely to broaden.

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- of interest
- of considerable interest

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